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THE CLINICAL PATHOLOGIST AS CONSULTANT AND TEACHER*

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"The practice of clinical pathology offers to the physician an unusual opportunity. It keeps him in intimate touch with disease in all its phases. It is a stimulus to medical research. It is scientific and accurate beyond the science of history taking or physical diagnosis. It is one of the most valuable aids to modern medical practice. American physicians are fortunate to have the assurance that the practice of clinical pathology is being maintained on a high plane." This quotation from an editorial which appeared in a recent number of the Journal of the American Medical Association carries with it a ringing challenge to the members of the American Society of Clinical Pathologists to strive vigorously to make the field of clinical pathology an even greater asset to the practice of modern medicine. To those who nurtured this Society in its infancy these words of praise should provide recompense for their relentless efforts to elevate the practice of clinical pathology to its present high plane.

A decade ago, when the idealism of Ward Burdick created this Society, the field of clinical pathology was an ill-defined territory in medical practice. In fact, during the first few years of the Society's growth some difficulty was encountered in arriving at a satisfactory definition of a clinical pathologist. Today, the clinical pathologist is recognized as a consulting physician whose chief interest lies in the diagnosis of disease by laboratory methods.

There may be a few persons who still think of the clinical pathologist as a glorified, overpaid technician. If there remains

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a clinical pathologist who still feels that he possesses such a status, he has only himself to blame. The day has long since passed, if in fact it ever existed, for the clinical pathologist to find it necessary to endear himself to one or two surgeons in order to hold his job. The growth of clinical pathology is in some respects not unlike that of surgery. Not so many decades ago the surgeon enjoyed the social status of a barber. Thanks to a dentist and a chemist, an opportunity was provided for a dominating intellectual group to bring the technic of surgery to its present perfection. It must be apparent to all that the heyday of surgery as the dominant field of medical practice has passed and that internal medicine and diagnosis are again destined to occupy the leading rôle. The recent strides in surgery have been largely due to the recognition by the surgeon that he can no longer travel alone, but that he must seek the collaboration of the physiologist, the pathologist, the bacteriologist, the biochemist and the physicist.

The renewed emphasis on diagnosis and rationally controlled therapy has brought the clinical pathologist to a place of prominence in medical practice. The past few years have witnessed an interesting blending of the fields of internal medicine and clinical pathology. The modern internist must possess an intimate working knowledge of the diagnostic and therapeutic aids provided by the clinical pathologist. By that same token, the clinical pathologist has been brought from the seclusion of his laboratory to the patient's bedside. The opinion of the modern clinical pathologist now ranks with that of any other medical consultant. It is natural, therefore, that as the field of clinical pathology continues to widen, the broad knowledge of the adequately trained clinical pathologist in the fields of hematology, serology, bacteriology, biochemistry, and histopathology will be more and more in demand by private practitioners in all fields of medicine. This natural evolution makes it imperative that the clinical pathologist should be thoroughly versed in clinical medicine. Without this background the information gained by laboratory studies is subject to misinterpretation and consequently does not redound to the welfare of the patient. That the clinical pathol-

ogist, whose long period of special training often exceeds that of many physicians in other special fields, should be compensated to the same extent as any other consultant, is a matter of simple justice.

With this growth of opportunity comes a greater degree of responsibility. The constant addition of new laboratory procedures demands the delegation of much of the purely technical work to lay technicians. Thanks to the unselfish and untiring labors of Dr. Philip Hillkowitz and the other members of the Board of Registry of Technicians of our Society, together with the cordial support of the Council on Medical Education of the American Medical Association and the American College of Surgeons, safeguards have been erected to prevent further invasion of the field by incompetent lay workers. It is the duty of all clinical pathologists who seek the respect and confidence of their medical brethren further to strengthen their position by eliminating inadequately trained or disinterested or dishonest lay technicians, and insist upon the certification of all capable workers by the Board of Registry.

The ever-widening scope of the field of diagnosis by laboratory investigation carries with it some danger of neglect of what Dr. Kenneth Lynch has aptly termed "the keystone of the practice of clinical pathology," namely, pathologic anatomy. Deliberated judgment, resulting from twenty years experience as a teacher of general pathology, director of a teaching hospital division of pathology and in the private practice of clinical pathology led Dr. Lynch to state that six years of training in tissue diagnosis is productive of less competency than six months in the other branches of clinical laboratory practice. With this thesis I am in complete accord. A thorough knowledge of gross and microscopic pathologic anatomy is perhaps the greatest single distinguishing characteristic which commands the respect of a clinical pathologist by his medical fellows. If we are to adhere for the present to the stipulation that a clinical pathologist is a physician who has "specialized in clinical pathology, bacteriology, pathology, chemistry, or other allied subjects for at least three years subsequent to graduation, who is in good standing and has been duly

licensed to practice medicine" (as defined by the Council on Medical Education and Hospitals of the American Medical Association) it seems reasonable to expect that at least two of the three years should be spent exclusively in pathologic anatomy. The objections which have been raised by various organizations, particularly in the diagnosis of neoplastic disease, would then be unjustified. The clinical pathologist must always remain a student. A month or two of special study of neoplasms every two or three years would be a profitable investment. Some of our own Fellows in the universities and larger clinics might consider the advisability of instituting such seminar courses, not only in the field of neoplasia, but also in hematology, serology, bacteriology and biochemistry.

Since it is now firmly established that the modern clinical pathologist is preëminently a consultant to other members of the medical profession there appears to be little excuse for the maintenance of such consultants at public expense. It would be as sensible to maintain at the expense of the taxpayer consulting surgeons, consulting pediatricians or consulting internists at the state capitol. Possibly the greatest excursion into the dark uncharted sea of state medicine has come as a result of the extraordinary development of certain state health laboratories, not infrequently under the direction of a person whose qualifications do not conform to the accepted definition of a clinical pathologist. The influence of the professional social worker has been an important factor in this unfortunate development. Since the publication of the report of the Committee on the Costs of Medical Care it has become apparent to practically every physician and to many sociologists that the time has come for the social workers to give the practice of medicine back to the doctors. The sensible and logical curtailment of the activities of the state health laboratories of Indiana provides a program for action by the Fellows of this Society in other states. When clinical pathologists in hospital and private practice have convinced the state medical associations that a higher type of service can be rendered by the physician-pathologist, the encroachment by state health laboratories on the field of clinical pathology will cease and the

state laboratories will revert to the purpose for which they were originally designed, namely, the control of transmissible disease and the provision of a diagnostic service for the indigent sick.

The clinical laboratory has become the scientific copestone of the modern hospital structure. It has been stated that "a hospital is only as big as its department of pathology." The hospital laboratory is the axis about which the scientific work of the hospital revolves. Upon the clinical pathologist, therefore, devolves the responsibility for the correlation and the dissemination of the scientific aspects of hospital medical practice. For this reason the clinical pathologist must be a teacher. The teaching activities of the alert clinical pathologist may assume several forms. The cheerful willingness correctly to interpret laboratory findings is one of the most fruitful forms of medical teaching, particularly as related to the welfare of the patient. The hospital staff conference and the clinico-pathologic conference provide perhaps the best method for the pathologist to contribute a large share to postgraduate medical education. The well-directed clinico-pathologic conference makes available the university idea of postgraduate medical education in every hospital with a capable clinical pathologist. He who does not fulfill this duty is missing his greatest opportunity to gain the respect and confidence of his medical brothers. Such conferences are capable of providing the greatest single stimulant to the scientific activities of the hospital. The intelligent correlation and interpretation of the information gained by postmortem examinations will quite naturally create interest in morbid anatomy and the clinician is provided with a real incentive to obtain permission for postmortem examinations on his patients.

The successful conduct of clinico-pathologic conferences requires consummate tact. If the emphasis is placed too heavily upon postmortem pathology, at the expense of clinical aspects, the interest of the average practitioner will not be aroused. The practice of some hospitals to make attendance at the clinico-pathologic conference compulsory to all staff members should be condemned. Attendance at the clinico-pathologic conference should be optional and induced only by the excellence of the

program. Such conferences should be held often enough to sustain interest. The weekly or bi-weekly clinico-pathologic conference, lasting for an hour or an hour and a half, but not longer, will accomplish this end. The logical place for the conference is in the hospital. The time for the conference should be chosen with a view to inconveniencing the smallest number of persons. The programs should be arranged so that a wide variety of subjects might be discussed at each conference, in order that the physicians in special fields might be induced regularly to attend the conferences. Recurrent discussion of the simple, commonly encountered diseases is of much greater importance than the presentation of rare and unusual diseases. The clinical pathologist is the natural and logical director of such conferences.

While it is generally admitted that the pathologist is usually "the court of last appeal," the shrewd and tactful pathologist will rarely exercise this prerogative. To give instruction to the informed physician is quite a different matter than the teaching of the uninformed layman or medical student.

Perhaps the greatest single asset to the clinical pathologist is an unfailing sense of humor. The shrewd clinical pathologist is constantly aware of the fact that physicians represent the greatest group of individualists of any professional field of endeavor. The exercise of restraint will accomplish much more than a practice of forcing his opinions and decisions upon his fellow practitioners.

The position of the clinical pathologist as consultant and teacher now rests upon a firm and substantial foundation. The evolution of medicine has placed the clinical pathologist in a commanding position. Much as the Council on Medical Education of the American Medical Association has raised the level of medical education to its present high plane, and as the American College of Surgeons and the American College of Physicians have succeeded in elevating the standards of surgical and medical practice, so the American Society of Clinical Pathologists is performing in a forceful manner much the same function as regards the elevation of the clinical pathologist to his rightful heritage.

THE AGGLUTININ CONTENT OF THE BLOOD FOLLOWING TYPHOID AND PARATYPHOID IMMUNIZATION*

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Most clinical pathologists have seen patients sent to their hospitals with a diagnosis of typhoid fever because of the presence of an otherwise unexplained fever and a positive Widal test. On further study some of these patients have been found to be suffering from another disease and the Widal reaction has been due to a previous vaccination. The widespread use of vaccination in military, school, and hospital circles, and even in the general population, has multiplied this rather serious source of error in recent years so that controlled observation of the agglutinin reactions of the blood of immunized persons are desirable. Recent literature reveals little information as to the duration or the strength of agglutinins in the blood following vaccination. However, Karl Meyer and Kilgore[3] report persistence of agglutinins for a period of ten months and summarize the literature up to the year 1917. They properly criticize much of the older work because of the technique employed, and the qualitative and quantitative variations of the antigens used both for vaccination and for the agglutination tests. More recently Hoffstadt and Thompson[2] report that in a series of persons immunized by the oral route, agglutinins persisted in a fair proportion of cases for five and fewer for nine months. Tests at later periods following vaccination were not reported by the above authors. Chambers[1] however, tested bloods from a series of war veterans vaccinated at various camps during the war and found appreciable agglutination in about half the cases for as long as thirteen years after inoculation.

* Read before the Eleventh Annual Convention of the American Society of Clinical Pathologists, New Orleans, Louisiana, May 6–9, 1932.

In the experiments herein recorded the agglutinin content of the blood of 120 vaccinated nurses and internes of the Buffalo City Hospital was determined in a period of two days, using the same flask of antigen for all the tests. Inasmuch as all the nurses were vaccinated by one of us (A.G.F.) with triple vaccine of the same type on their entrance into training, we were able to obtain bloods from small groups from the various classes immunized at periods varying from twenty-three days to nine years after the date of the last of three weekly injections.

METHOD OF OBSERVATION

The vaccine used was the triple vaccine supplied by the New York State Board of Health Laboratory, who obtained the strains from the Army Medical School, and contained one billion typhoid (Rawlins) and 750 millions each of paratyphoid A (Kessel) and paratyphoid B (Rowland) bacilli per cubic centimeter. The doses were 0.5 cc., 1 cc. and 1 cc. given subcutaneously at weekly intervals. All received three full doses. None had had typhoid fever or previous inoculations. The antigen used in the agglutination tests was prepared in a two liter flask of Liebig extract broth containing 0.3 per cent meat extract, 0.5 per cent sodium chloride and 1 per cent Witte's peptone, adjusted to give a pH of 7.3 after autoclaving, to which was added sufficient typhoid bacilli (N. Y. State No. 305) to yield a satisfactory growth. After eighteen hours incubation the culture was killed by adding 1 cc. of 40 per cent formaldehyde per liter of antigen and allowed to stand in the icebox for two weeks before using. Control tests showed proper agglutination with standard serum supplied by the New York State Laboratory and no agglutination at dilutions of 1:20 or above, with serums of normal non-inoculated individuals.

The serums to be tested were inactivated in a water bath at 56°C. for half an hour, and dilutions of 1:10, 1:20, and upward by multiples of two to include the anticipated agglutination range, and to 0.5 cc. of each dilution 0.5 cc. of the antigen was added. The tubes were placed in a water bath at 38°C. for two hours, and read after standing in the icebox overnight. The titers given in table 1 represent the highest dilution at which agglutination was visible macroscopically.

Table 1 shows the number of serums agglutinating at the various highest dilutions at the different time intervals following the last of three injections. All of the serums studied show agglutinins ranging from a titer of 1:20 to 1:1280. The titer showed an average of 1:320 to 1:640 at the end of twenty-three days and 1:80 to 1:160 at the end of eleven months, but agglutinins were

TABLE 1

NUMBER OF SERUMS AGGLUTINATING TYPHOID BACILLI AT VARIOUS DILUTIONS AT DIFFERENT TIME INTERVALS AFTER VACCINATION

TIME	1:20	1:40	1:80	1:160	1:320	1:640	1:1280	TOTAL SERUMS
23 days				3	10	8	1	22
32 days				4	5	3		12
4½–5 months			4	8	2	4	2	20
9 months		2	4	6	3	3		18
10½–11 months		1	2	2			1	6
18 months		2	2	6	1		1	12
2 years			1	1				2
26 months	1		3	2				6
2½ years			3	3	1			7
3 years			2		1			3
3½ years			2	1				3
4 years		1	1	1				3
5 years			2		2			4
6 years				1				1
9 years				1				1
Total serums...								120

TABLE 2

AGGLUTININ TITERS OF TWENTY-THREE SERUMS AGAINST TYPHOID AND PARATYPHOID BACILLI AT VARIOUS TIME INTERVALS

SERUM	TIME	TYPHOID	PARATYPHOID A.	PARATYPHOID B.	SERUM	TIME	TYPHOID	PARATYPHOID A.	PARATYPHOID B.
1	4½ months	1:1280	1:20	1:160	13	9 months	1:160	1:20	1:80
2	4½ months	1:640	1:40	1:40	14	11 months	1:1280	1:80	1:80
3	4½ months	1:640		1:80	15	18 months	1:160	1:20	
4	4½ months	1:160	1:20	1:40	16	18 months	1:160	1:40	1:40
5	4½ months	1:160	1:20	1:40	17	18 months	1:40		1:20
6	4½ months	1:160	1:20	1:40	18	30 months	1:160	1:40	1:80
7	4½ months	1:160	1:20	1:80	19	30 months	1:80	1:40	1:40
8	4½ months	1:160	1:40	1:320	20	3 years	1:80	1:40	1:160
9	4½ months	1:80	1:40	1:40	21	3 years	1:80		1:160
10	9 months	1:320	1:40	1:160	22	4 years	1:80	1:40	1:40
11	9 months	1:160	1:80	1:80	23	5 years	1:80	1:20	1:40
12	9 months	1:160	1:20	1:80					

present in clinically important dilutions for a period of many years, including one serum agglutinating at 1:160 at nine years and one at a similar dilution six years after immunization.

A series of twenty-three sera were tested for agglutinins for paratyphoid A (N.Y. State No. 17) and paratyphoid B (N. Y. State No. 18) bacilli with antigen prepared in a method similar to that outlined for the typhoid strain mentioned above. The results in table 2 show that on the average there was less agglutinin formed against the paratyphoids than against typhoid bacilli, and usually higher paratyphoid B titers were produced than paratyphoid A. However, there was no definite regularity as to the response to the three organisms since some serums showed high typhoid titers and low paratyphoid titers, and in an occasional case this relation was reversed.

SUMMARY AND CONCLUSIONS

Agglutination tests conducted simultaneously with the same flask of antigen on serums of 120 nurses and internes immunized by three weekly subcutaneous injections of triple typhoid paratyphoid A and B vaccine furnished by the New York State Department of Health revealed the presence of typhoid agglutinins in a dilution averaging 1:320 to 1:640 at the end of twenty-three days following the last injection.

Tests at longer intervals of several months and to five to nine years demonstrated persistence of agglutinins in all the serums studied in lower, but clinically significant amount, for example, 1:160 after six and nine years, respectively.

Agglutinins against paratyphoid bacilli were demonstrated at titers averaging somewhat lower than the corresponding titer against the typhoid bacillus.

In evaluating a positive agglutination test against typhoid or paratyphoid organisms, the history of prophylactic immunization must be considered, even though many years have elapsed since the inoculations.

We wish to thank Dr. Benjamin Smallman, Miss Sophia Zurette, and Mrs. Marjorie Bauckus Cargill for their aid in preparing sera and setting up the tests.

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CHOLECYSTECTOMY AS SEEN BY THE SURGICAL PATHOLOGIST

Report of 223 Cases

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The types of pathology which, occurring in the gallbladder, have given rise to characteristic symptoms and to surgical removal of the gallbladder, have been described in detail by Baumgartner.[1] Becker[2] and Mentzer[5] have each reported the incidence of gallbladder lesions in a series of postmortem examinations. Surgeons have presented their view of the indications for cholecystectomy repeatedly, and some have told of the results obtained subsequent to this operation. I have not found reference to a surgical pathologist presenting the question of why normal gallbladders appear in his laboratory, or what their significance may be.

In studying this series of 223 gallbladders which have come to me from nineteen surgeons in five hospitals, I have tried to correlate preoperative diagnoses, pathological findings, and clinical results. The removal of appendices, and the operative treatment of peptic ulcer, as these have been done in addition to the removal of the gallbladder have also been noted. The surgeon who is irritated when the pathologist fails to find sufficient evidence of disease in the removed gallbladder, the pathologist who wonders whether the surgeon is not sometimes overenthusiastic about cholecystectomy and the patient who has to live on without a gallbladder, normal or diseased, will be concerned with this study.

In histology and gross anatomy the gallbladder differs somewhat from the appendix, with which it competes as a cause of digestive disturbance which can be removed by surgery. Its mucosa contains no lymphoid tissue, and such mucus as is fur-

nished to lubricate its surface comes from the columnar cells which cover it, rather than from definite gland structures. The greater part of the wall consists of a fibromuscular layer, in which poorly developed bundles of smooth muscle interlace in a rather loose fibrous stroma. The serous and subserous layers differ in no way from the same tissues throughout the peritoneal cavity.

The gallbladder is not subject to the gross fecal contamination which carries anaerobes and a multitude of more or less virulent bacteria to the appendix. As a result acute inflammations are comparatively rare in the right upper quadrant of the abdomen. On the other hand, the gallbladder is, as a storage reservoir, subject to mechanical obstruction of its exit, and to precipitation of salts from its contents. These more or less continuous irritants are at least partially responsible for the presence of scattered lymphocytes in the gallbladder wall, and for the slowly increasing predominance of fibrous tissue over muscle, which we know as chronic cholecystitis. Bacteria, entering from liver, duodenum, lymph or blood stream, may combine with the mechanical effect of stones, and produce acute lesions. Malignancy develops occasionally.

Making the data as simple as possible without sacrificing the accurate accomplishment of our purpose, I have grouped the cases in this series, according to the preoperative diagnoses, as (1) chronic cholecystitis (without stones); (2) cholelithiasis; (3) acute cholecystitis, and (4) peptic ulcer. The demonstrable pathology is divided into (1) chronic cholecystitis; (2) cholelithiasis; (3) carcinoma, and (4) no pathology found in the gallbladder. The fourteen cases of acute inflammation, and nine of papilloma, have been placed with the chronic conditions upon which they have been superimposed.

The records show that diagnoses have been made from the usual symptoms, physical findings, and X-Ray reports, with or without the use of dye tests. Gallbladders have been removed after a diagnosis of peptic ulcer chiefly for three reasons, gross thickening of the wall, the presence of adhesions about the gallbladder, and failure of the viscus to empty easily under compression.

The comparison of clinical and pathological findings is shown

in table 1. One hundred sixty-three cases were diagnosed "chronic cholecystitis," or "gallbladder disease." Of these, ninety-seven showed infiltration with lymphocytes and/or the

TABLE 1

PREOPERATIVE DIAGNOSIS	PATHOLOGICAL DIAGNOSIS		APPENDECTOMIES			
			Normal	Acute	Chronic	Previous operation
Chronic cholecystitis (gallbladder disease), 163 cases	Chronic cholecystitis	97	10	1	33	18
	Peptic ulcer 1					
	Papilloma 7					
	Acute inflammation 4					
	Cholelithiasis	46	6	0	10	2
	Acute inflammation 6					
	Carcinoma 1					
	Carcinoma	2	0	0	1	0
	Epidermoid 1					
	Adenocarcinoma 1					
	No pathology found in gallbladder	18	5	2	7	2
Cholelithiasis, 36 cases	Chronic cholecystitis	3	1	1	0	0
	Cholelithiasis	32	4	0	8	4
	Acute inflammation 4					
	Papilloma 2					
	No pathology found in gallbladder	1	1	0	0	0
Acute cholecystitis	Acute cholecystitis with stones	4	1	1	0	0
Peptic ulcer, 20 cases (7 found)	Chronic cholecystitis	14	1	0	4	3
	Papilloma 1					
	Cholelithiasis	1	1	0	0	0
	No pathology found in gallbladder	5	0	0	2	2
Totals		223	30	5	65	31

fibrosis which I have called chronic cholecystitis. In addition, four of these patients had acute inflammatory changes, seven had developed papillomata in the mucosa, and one patient had a peptic ulcer in addition to cholecystitis.

In forty-six of this group gallstones were present, but had not been mentioned in the preoperative record. Six acute inflammations and one with squamous-cell carcinoma were associated with stones. In addition to the carcinoma complicating gallstones, one adenocarcinoma in a gallbladder free from stones was found. In eighteen gallbladders from this group of patients I did not find any tissue change which was considered pathological.

TABLE 2

CLINICAL RESULTS		PATHOLOGY						
		Cholecystitis	Stones	Papilloma	Carcinoma	Peptic ulcer	None found	Appendix removed
After 1 to 10 years:								
Cured	76	33	34	5	0	2	9	45
Improved	31	17	8	0	1	2	5	20
No improvement	41	27	7	0	1	3	6	23
Less than 1 year:								
Improved	33	16	16	1	0	1	1	19
No improvement	4	3	0	0	0	0	1	1
Deaths within 30 days	9	5	4	0	0	0	0	3
Due to:								
Diabetes 1								
Pneumonia 1								
Ileus 1								
Hepatitis 1								
Peritonitis 1								
Cause not given 4								
Totals	194	101	69	6	2	8	22	111

Among thirty-six cases diagnosed as "cholelithiasis" the agreement was much better. In only four were the stones not present, and three of these showed the changes of chronic inflammation.

The four patients diagnosed as having "acute cholecystitis" all had gallstones, and an acute inflammatory process in addition.

I have mentioned above the reasons given in the operative records for removing twenty gallbladders after diagnoses of peptic ulcer. Opinions necessarily will differ as to whether or not find-

ing five "normal" gallbladders in this group, nearly three times the proportion found in the other cases, has any significance. Graham and his associates[4] state that pressing upon the gallbladder as a test of patency of the ducts is inadvisable; and Blond[3] believes that valvelike folds of mucosa in the cystic duct may oppose violent attempts to expel the bile. Perhaps this surgical habit should be revised.

One hundred thirty-one patients, or 59 per cent of the total, lost their appendices either at the time of the cholecystectomy or in previous operations. This fact is of some interest in connection with the clinical results which followed these operations.

We have been able to follow up 194 of these patients, and secure from the histories or from the surgeons, reports as to relief from the symptoms which brought the patients to operation. Considering that a year should be allowed for the subsidence of the hepatitis which accompanies most cases of gallbladder infection, and for clinical readjustment, I have made two groups, one consisting of those patients whose condition is known for from one to ten years after operation, the other of patients operated upon since July 1st, 1931.

Fifty-one per cent report cures after one year, and 21 per cent are improved. The remaining 28 per cent, of the older group still have their original symptoms. The thirty-seven patients operated upon during the past year have been more fortunate, 90 per cent of them reporting relief from symptoms. Figuring only cases having gallstones, 84 per cent of the entire series are cured or improved. Nine of the patients have died within thirty days after operation, 4 per cent of the total series.

If we combine the records of all the patients whose present condition we know, we find that seventy-six, or 39.2 per cent are cured; sixty-four, or 33 per cent are improved; and forty-five, or 23.2 per cent are not improved.

But what of the normal gallbladders? I have found them in 12 per cent of the "cured" list, in 10 per cent of the "improved," and in 15 per cent of the unimproved: not an impressive difference. Perhaps this may be interpreted as evidence for the existence of "cholecystopathy," a condition of abnormal metabolism

without anatomical change. Certainly no facts have been brought out to discourage the surgeon from undertaking cholecystectomy when his diagnostic measures indicate probable gallbladder disease. The pathologist must agree that patients may receive symptomatic relief after the removal of gallbladders free from apparent lesions.

One other question occurs. Is it possible that coincident appendectomy or pyloroplasty helps in this cure of patients whose gallbladders have not shown disease? There have been 111 appendectomies, or 57 per cent of the number whose clinical condition was known. This compares well with the 60 per cent of the cured, 60 per cent of the improved, and equally well with the 54 per cent of unimproved, who have had the appendix removed. Such figures suggest that appendectomy may add slightly to the chance for cure, but are not convincing. Among the normal gallbladders there are fifteen which, aided by eleven appendectomies and two ulcer operations, are reported as cured or improved. Seven similar patients, from whom five appendices and one ulcer were removed, are not improved. This appears to show that the extra surgery which went with the removal of the anatomically normal gallbladders did not increase the patients' chances for recovery, nor did it lessen such chances.

One may conclude from this study that patients with gallstones have been most certain (84 per cent) to improve after cholecystectomy; and that 65 per cent of the chronic cholecystitis cases have been relieved. The general average of cures and improvement in the series is 72.2 per cent. Seventy per cent of the normal gallbladder removals were clinically successful, and this improvement was not increased by coincidental surgery of appendix or ulcer.

SUMMARY

(1) Cholecystectomies done on 223 patients are compared with respect to clinical and pathological findings, with especial attention to the result when the gallbladder has shown no anatomical pathology.

(2) Twenty-four, or 11 per cent of the gallbladders removed

failed to show any anatomical pathology, gross or microscopical. Of these, eighteen were from patients diagnosed as having chronic cholecystitis, or "gallbladder disease," one was removed under a "gallstone" diagnosis and five were from cases in which peptic ulcer was suspected.

(3) Reports were secured concerning the clinical condition of 194 patients one year or more after operation, or up to July 1st, 1932. Of these, seventy-six, or 39.2 per cent are reported cured, sixty-four, or 33 per cent improved and forty-five, or 23.2 per cent not improved. The mortality within thirty days after operation was 4 per cent.

(4) The "normal" gallbladders were distributed without significant variation between the cured, improved, and unimproved groups.

(5) Coincident appendectomy or ulcer operation appears to have no influence upon the prospect for cure after the removal of nonpathological gallbladders.

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CLASSIFICATION AND PATHOGENICITY OF CERTAIN MONILIAS*†

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The rôle of monilia in disease has been in controversy since the description of Langenbeck (1839) of the "thrush" fungus. The most common lesions are located on the buccal mucosa and the mucous membranes of the larynx, eosphagus, and vagina. M. Gubler[7] said that they never attack the mucous membrane of the bronchi because of the alkaline secretion. Robins[3] made very extensive clinical observations on the nature of the membrane found in cases of thrush and the method by which it is produced. He formulated the theory that the fungus requires an acid medium in which to propagate and that this medium is supplied by acid secretion of the inflamed buccal mucosa. He considered the fungus a harmless parasite adhering to the surface of the epithelium which proliferates and desquamates because of the inflammation. The membrane produced under such conditions is composed of desquamated epithelial cells, tenacious mucus, and tangled masses of mycelium, and is in no sense an inflammatory exudate. Gubler was of the same opinion and said that he never saw the fungus spread into the bronchi where the secretions are alkaline but in a few cases he saw it on the mucosa of the stomach and small intestine. Vogel,[24] however, was of the opinion that the thrush fungus sometimes produces true pseudo-membranes such as those seen in cases of diphtheria. These clinical investigators made no distinction between the different species of monilia that are associated with thrush.

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Herf,[8] reported twenty-six cases of vaginitis due to monilia. He stated that the organisms produced severe inflammatory reactions which were associated with burning and itching. Most of his cases occurred during the course of pregnancy. He made cultural studies and identified two types of monilia, *M. albicans* and *M. candida.*

Plaut[15] studied *M. albicans* and *M. candida* in an effort to find distinguishing characteristics for the separation of the "thrush" fungi, *M. albicans,* from *M. candida,* isolated from decaying wood by Bonorden.[2] These experiments included studies on the pathogenicity of these two species. He used young chickens, pigeons and rabbits. Two methods of inoculation were used for the fowls, by streaking cultures over the mucosa of the beak and crop, and by sewing together a wound made in the crop by a scalpel with silk threads which had previously been soaked in a suspension of these organisms. The young fowls died within four or five days but older ones withstood the infection and recovered after several weeks. He failed to produce lesions in dogs by any method and was only rarely successful when he inoculated rabbits intravenously. He concuded that the thrush fungus and *M. candida* are identical.

Craik,[5] isolated both *M. albicans* and *M. candida* from cases of thrush.

Castellani's[3,4] report of the frequency of broncho-moniliasis in the tropics created widespread interest. He recognized the infection as manifesting varying degrees of severity and described the disease as being mild, severe and very severe. His studies were confined to the cultural reactions of the organisms isolated from sputum. He reported no postmortem examinations and no animal experimental work.

Ashford[1] isolated cultures of monilia from cases of sprue and called the organism *M. psilosis.* He was able to produce generalized moniliasis in rabbits and guinea-pigs by intravenous injections and was able to exalt the virulence of the cultures by repeated passage through animals. When fed to guinea-pigs organisms whose virulence had been increased by animal passage produced stomatitis and diarrhea.

The literature contains many case reports associating various species of monilia with bronchitis, pneumonia, asthma, vaginitis, and skin lesions. From the tropics Sen[17], Paramanand,[12] and Pijper[13] have contributed to this literature and in this country Simon,[19] Steinfield,[20] Johns,[9] Shaw,[18] Plass,[14] Gilbert[6] and others. Their reports are, however, not accompanied by animal experimentation except in a few instances and we have seen no postmortem reports. The organism isolated have been grouped according to Castellani's classification or have been given new names.

One of us[23] reported eighteen cases of bronchomycosis, recurring attacks of pneumonia going on to bronchiectasis, and varying grades of bronchitis, associated with sputum laden with monilia fungi. In this report no attempt to classify the organisms was made. The cases were divided clinically into very mild, moderately severe and severe infections. One patient in the group died but postmortem was refused.

Nye, Zerfan and Cornwell[11] working with cultures isolated from the stools of apparently normal people and from others afflicted with various diseases killed rabbits by intravenous inoculations with cultures classified as Parasaccharomyces A. All other types of parasaccharomyces (monilia) they found to be nonpathogenic for rabbits even in very large doses. They concluded that following intravenous inoculation of large doses, Parasaccharomyces A is mildly pathogenic for rabbits and that occasional human infections may have occurred.

Stovall and Bubolz[21] classified monilia isolated from sputum in cases of bronchitis, pneumonia and asthma, and showed that the organism isolated could be classified into three species by fermentations and colony formation on malt agar. They[22] reported a further study of organisms isolated from sputum and also cultures secured from the American Type Culture Collection. They found that all of these cultures could be classified into three species on the basis of fermentations, reaction in calcium lactate milk and colonies on malt agar (table 1).

It is apparent from this very brief review of the literature that the notion concerning the pathogenic qualities of the various spe-

cies of monilia is vague and that the conflicting reports are in all probability due to the failure of the investigators to recognize the different species.

In view of the conflicting opinions found in the literature and since we were able to classify more than 150 organisms associated with various diseases into three species, Type I, Type II, Type III, we decided to determine the reaction of animals to each of the three types with the idea that further distinctive features might be revealed by characteristic animal reactions for each species and that the reactions would reveal the nature of the disease process.

TABLE 1

DIFFERENTIAL CHARACTERISTICS OF THE THREE TYPES OF MONILIA

	MALTOSE	SACCHAROSE	MILK	MYCELIAL COLONIES MALT AGAR (48 HOURS)
Type I.....	Acid	Acid	0	+
Type II (*M. albicans*)....	Acid and gas	Acid	Coagulation	0
Type III (*M. candida*)...	Acid and gas	Acid and gas	0	++

MATERIAL AND METHODS

Five cultures of each type were selected for the work. Since we have found in the American Type Culture Collection, organisms already named which typify each of our groups, we have in this paper used the name of the type culture which typifies the group rather than the group number. In group one, typified by *M. parapsilosis*, four of the cultures are from our own collection and one from Johns Hopkins University. The other two groups, typified by *M. albicans* (Type II) and *M. candida* (Type III) contain two strains each from our own collection and three each from the American Type Culture Collection. A complete history of each culture is recorded in table 2.

Cultures were grown on malt agar for twenty-four hours at 37°C. and washed down with sterile normal salt solution. These suspensions were shaken in flasks with glass beads and standardized for the number of fungus cells per cubic centimeter by counts in a hemocytometer. No mycelium was produced on this medium in the incubation period used.

Rabbits, guinea-pigs, white rats and mice were the animals used and the method of inoculation was chosen to suit the purpose of the particular experiment. Thus intravenous injections of measured doses of the three species were given to rabbits in order to determine the lethal and morbidity dose of each by

TABLE 2

NUMBER	SOURCE	CLINICAL DESCRIPTION OF CASE AND REMARKS
		Type I *M. parapsilosis*
35221	Sputum	Mild but persistent bronchitis. Sputum repeatedly negative for tubercle bacilli. Wassermann negative. No further report
38746	Sputum	Male, age 40, farmer; lost 15 pounds weight; sick three years; two ounces of sputum in 24 hours. Wassermann negative; sputum negative for tubercle bacilli. Died. No autopsy
M. parapsilosis		Furnished by J. H. Lamb, Johns Hopkins University, Department of Pathology
50858	Sputum	Male, age 36, a laborer. Four months before pulmonary symptoms had ringworm on cheek; sick two years; x-ray diagnosis: interlober empyema or abscess. Reported year later blastomycosis from another laboratory. Sputum negative; Wassermann Negative. Recovered
36255	Sputum	Chronic bronchitis. No response to inquiry about patient
		Type II *M. albicans*
33691	Sputum	Male, age 45, sick two months; sputum negative for tubercle bacilli; severe cough; large ulcer on soft palate, upper and lower lip; fungus in sputum, and fluid from ulcers on lips; dullness over lower right chest posteriorly and anteriorly. Died. No autopsy
22353	Sputum	Male, age 35, mild bronchitis with elevation of temperature for two months. Recovered
4135	American Type Culture	*M. pseudo-tropicalis* Castellani
2112	American Type Culture	*M. albicans*; Natl. Coll. Type Cul., Lister Institute, 714. Isolated by Craik from case of thrush
2117	American Type Culture	*M. psilosis* Ashford. Natl. Coll. Type Culture Lister Inst. From J. T. Duncan, London School for Trop. Medicine. Isolated from feces of acute case of sprue
		Type III *M. candida*
23669	Sputum	No record of patient
14999	Buccal mucosa	Membrane covered the mucosa of the cheek, gums and lips to the edge of the skin. Thrush. Patient anemic; membrane present one year
2113	American Type Culture	*M. candida* Bonorden. Natl. Coll. Type cultures; Lister Institute, 922, Tanner Collection
1369	American Type Culture	C. Neuberg, Berlin, Germany (Bonorden Handb. p. 76, Fig. 86, 1857) Thom and Church collection, 4472-2
750	American Type Culture	*M. tropicalis* Castellani; Aldo Castellani, Tulane Univ., isolated 1909

this method. In order to test the tissue invasiveness, local injections were made beneath the skin, into various viscera, into the nasal sinus, and into muscles.

In this paper it is not feasible to give in detail all of the experiments that were carried out or to include the results obtained with guinea-pigs, white rats or mice. That will be reported elsewhere. We have, therefore, set forth in this paper the outstanding features of the results of the studies with rabbits.

TABLE 3

DOSE DIFFERENCES OF MONILIA SPECIES

(Dose in millions per 100 grams body weight)

SPECIES	LETHAL DOSE	MORBIDITY DOSE
	millions	*millions*
Monilia parapsilosis, Type I	None	200*
Monilia albicans, Type II	1.5	0.5
Monilia candida, Type III	35.0	6.0

Dose variability of Type II

STRAIN	LETHAL DOSE	MORBIDITY DOSE
	millions	*millions*
4135	1.5	0.5
2112	1.5	0.5
22353	1.5	0.5
2117	3.0	1.0
33691	6.0	2.5

Dose constancy of Type III

STRAIN	LETHAL DOSE	MORBIDITY DOSE
	millions	*millions*
2113	30.0	5.5
1369	25.0	5.0
750	30.0	5.5
23669	35.0	6.0
14999	35.0	6.0

* No lesions.

DOSAGE

In connection with previous work we had observed that some rabbits died within several hours or days following intravenous inoculations and others tolerated approximately the same dose without ill effect. We did not then know the species of organism used. The average lethal and morbidity intravenous dose for each of the three species and for each of the strains within the species is shown in table 3.

M. parapsilosis demonstrated no pathogenicity in these experiments. We ran the doses extremely high in attempts to establish the tolerance of the animal. The largest dose administered was three billion organisms suspended in 10 cc. of salt solution to a rabbit weighing 1830 grams. The rabbit showed nothing more than a slight elevation of temperature and leukocyte count for twenty-four hours. Postmortem examination of animals injected with the five cultures in this species revealed no lesions.

These results show a wide variability in the lethal and morbidity doses for these three species of monilia, the variation being so distinct for each that the identity of the organism can be predicted on the basis of intravenous dose required to kill a normal healthy rabbit. Thus it is seen that *M. parapsilosis* causes no change in the behavior of rabbits and no lesions at postmortem in doses of three thousand million. *M. albicans* on the other hand killed regularly in doses varying from twenty-five to seventy-five million and morbidity doses varying from ten to fifty million produced acute illness, and extensive lesions in various organs with eventual recovery or death of the animal. *M. candida* shows a sharp contrast to the other two species. It produces death if very large doses are used, six hundred million to eight hundred million, and a few chronic lesions in doses of two hundred to three hundred million. Thus contrasting *M. candida* with *M. albicans* it was necessary to inject five to fifteen times more cells of the former than the latter to cause death or to produce lesions without causing death.

CLINICAL COURSE

In the clinical course the differentiation between the three species was clearly evident and the more virulent effects of *M. albicans* were demonstrated. No rabbits manifested more than a slight rise of temperature and leukocytes for twenty-four hours when inoculated with even massive doses of *M. parapsilosis*. Those receiving relatively small doses of *M. albicans* became very ill, lost weight rapidly and died in eighteen hours to eight days. Death was often preceded by suppression of urine and convulsive seizures. Those to which sublethal doses were administered became very ill

for the following five to eight days and then began to recover but most of them never regained their normal weight. The temperature rose from 103° to 105° and remained up for several days to a week and gradually declined to normal. The leukocyte count revealed the overwhelming effect of this organism. For twenty-four to forty-eight hours following the inoculation there was a marked leukopenia. Unless the animal went into uremia and died the count began to rise and the next day or two a marked leukocytosis appeared and lasted for two weeks or longer. Weight loss and emaciation was marked and all the animals except the ones inoculated with culture No. 33691 became uremic. The evidence of uremia was based on suppression or decreased quantity of urine, elevated non-protein nitrogen and muscle twitching or convulsions. One rabbit showed 260 mgm. of non-protein nitrogen per 100 cc. of blood on the sixth day following inoculation and died. Another rabbit developed a non-protein nitrogen blood retention of 200 mgm. by the sixth day when there were signs of uremia but by the eleventh day the non-protein nitrogen had fallen to 67 mgm. and the animal recovered.

M. candida produced a very much less stormy course. Organisms of this species resulted in a rise of temperature for a few days in no way different from that described for *M. albicans*. The leukocytosis was milder and leukopenia did not occur. The urinary output remained normal; only traces of albumen were encountered and the microscopic examination revealed only occasional leukocytes and casts. Fungus cells were not infrequent but no mycelium was found as it was in animals inoculated with *M. albicans*. The non-protein nitrogen of the blood was not elevated.

GROSS AND MICROSCOPIC EXAMINATION OF TISSUES

It is to be expected that postmortem examination following such widely varying clinical courses would reveal marked differences in tissue reactions. *M. parapsilosis* produced no gross or microscopic tissue changes. Sections of the kidney, lung and liver removed from animals killed within two to twenty-four hours following inoculation showed fungus cells but no mycelium and no budding forms and there was no cellular reaction in the tissue.

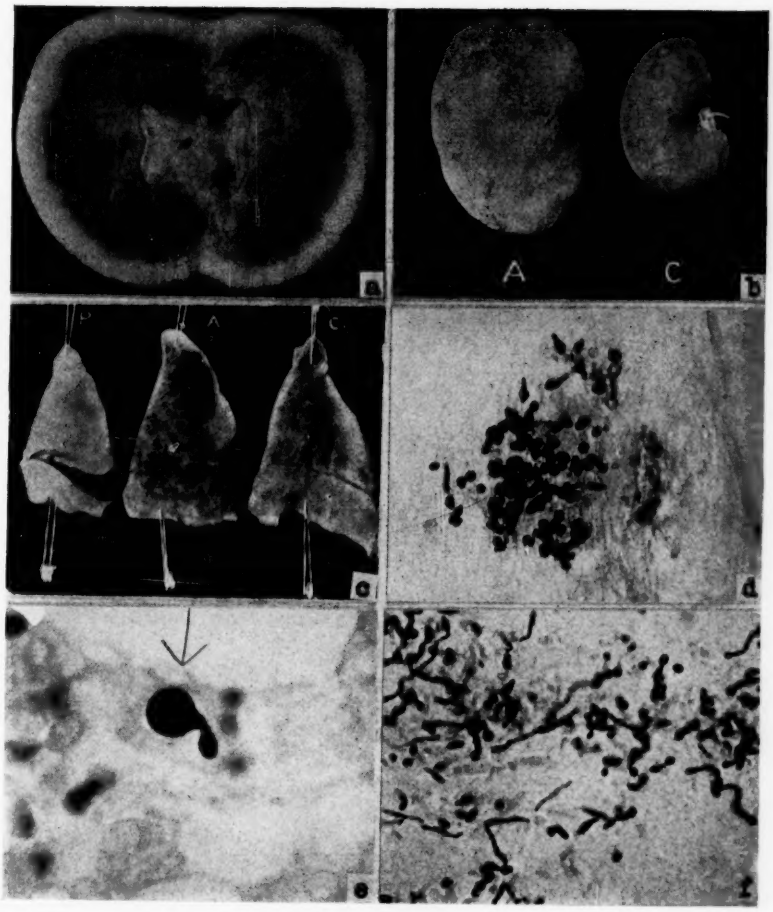

FIG. 1

a. Large white kidney of rabbit 23 inoculated intravenously with 52 million cells of *Monilia albicans* (Type II) and killed 6 days later. Non protein nitrogen 200 mgm. per cent. Kidney two and one-half times larger than normal. Thick, anemic cortex with miliary abscesses sharply demarcated from congested medulla.

b. A: *M. albicans* infected kidney; weight of rabbit 1585 grams, dose 62 million, killed on fifth day. C: *M. candida* infected kidney; weight of rabbit 1665 grams, dose 229 million, killed on ninth day.

c. Lungs of rabbits inoculated intravenously with the three types of monilia. P: *M. parapsilosis;* dose 3,000 million. Very rare petechial hemorrhage. A: *M. albicans;* dose 60 million. Numerous petechial hemorrhages. C: *M. candida;* dose 275 million. Few petechial hemorrhages.

d. Gall bladder lesions showing budding and elongated *M. albicans*. Rabbit inoculated intravenously.

e. Budding *M. albicans* in alveolar wall of a rabbit's lung.

f. *M. albicans* in a brain abscess. Mycelia; lateral and terminal conidia.

M. albicans showed characteristic reaction in the lungs and kidneys. The liver, however, proved resistant, rarely showing gross lesions although the gall bladder bile contained abundant mycelium and in some cases abscesses in the wall from which the fungus was isolated (fig. 1, *d*). The kidneys were two to two and a half times normal size, the capsule was tense and the surface appeared very granular due to numerous small greyish-white abscesses pin point to pin head in size (fig. 1, *a*). The cut surface showed a pronounced contrast between the cortex and medulla (fig. 1, *b*). The cortex was greatly thickened, appeared almost white, and was thickly studded with minute abscesses (fig. 2, *a*). The normal cortical markings were absent. The medulla appeared markedly congested and contained a few small abscesses. This description is characteristic for the kidneys of those animals that either died or were killed within the first eight days following the inoculation.

The microscopic examination of sections from these kidneys showed the process to be acute, exudative in type and revealed many fungi in the lesions which appeared not only as single or budding cells but also as strands of mycelia (fig. 2, *c*).

The lungs of rabbits which died or were killed within forty-eight hours after inoculation were characterized by numerus subpleural

FIG. 2

a. Kidney of rabbit inoculated intravenously with 50 million *Monilia albicans* cells and killed two days later. Miliary abscesses in cortex.

b. Kidney of rabbit inoculated intravenously with 330 million *Monilia candida* cells and killed on ninteenth day. Wedge shaped granulomatous areas involving medulla and lower zone of cortex.

c. Mycelia of *M. albicans* in an abscess of the kidney cortex. Modified Gram stain.

d. *M. candida* in kidney lesion. No mycelia formed. Modified Gram stain.

e. Early formation of a mycelium in the intertubular capillary of the kidney. Rabbit killed four hours after inoculation of *M. albicans*.

f. Mycelia with lateral and terminal conidia. Rabbit killed 40 hours after intravenous inoculation of *M. albicans*.

g. Long mycelia in glomerulus and outside of glomerulus. Rabbit died on third day; inoculated with *M. albicans* into the nasal sinuses.

h. Miliary abscesses in skeletal muscle (thigh muscle). Rabbit died on the 4th day after intravenous inoculation of *M. albicans*.

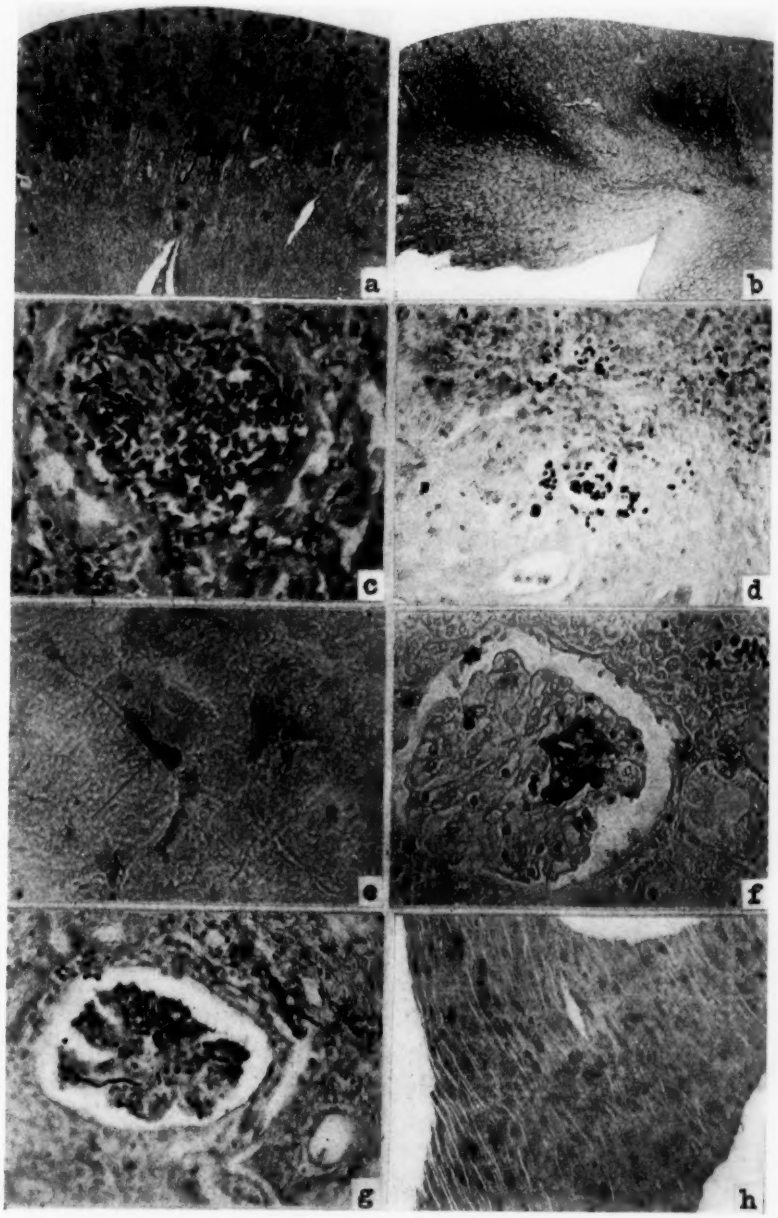

FIG. 2

petechial hemorrhages (fig. 1, *c*), and the cut surface revealed similar hemorrhages ranging in size from a pin point to several millimeters. Thrombosis of the large vessels was seen occasionally; eight per cent of the animals in this group died of pulmonary thrombosis. If the animal lived the petechiae later disappeared and the lung appeared grossly normal.

Microscopic examination of the lungs removed in the first twenty-four hours after inoculation showed a thickening of the alveolar walls. This thickening was not uniform through the alveolar wall but was distributed along the walls like knots in a string. These nodules were capillary thrombi by fungi accompanied by a cellular reaction in the tissue composed of polymorphonuclear leukocytes and mononuclear cells. However, they were not all thrombi; many were cellular reactions around groups of fungi in the tissue. Exudation and hemorrhage into the alveolar spaces caused small, patchy, irregularly distributed consolidations similar to the first stages of bronchopneumonia.

Gram stain demonstrated the presence of budding fungi and mycellia in these lesions (fig. 1, *e*).

Lesions in other tissues throughout the body were frequent. Multiple lesions in the skeletal muscle (fig. 2, *h*), heart muscle and various viscera occurred with the more virulent cultures.

Animals inoculated with *M. candida* showed fewer lesions and fewer structures involved in spite of doses five to fifteen times larger than with *M. albicans*. The kidneys and lungs were the only organs or tissue affected. The kidney, however, was always normal in size, or only slightly enlarged, the capsule stripped with ease, displaying a smooth, pale red surface with an occasional pin point to pin head size greyish white, slightly elevated area (fig. 1, *b*). The cut surface showed normal parenchymal markings. The cortex was not thickened and contained only an occasional wedge-shaped greyish white area which extended through the medulla. There were also other greyish white areas in the medulla.

The microscopic examination revealed an explanation of the striking difference of the kidneys in these animals and those injected with *M. albicans*. The lesions were of a chronic granulo-

matous type, being characterized by infiltrations of lymphocytes, eosinophilic leukocytes, plasma cells, monocytes and a few polymorphonuclear leukocytes. Perivascular lymphocytic infiltrations were not uncommonly seen. The lesion rarely went on to necrosis. Cellular reactions were absent in all rabbits killed two and a half hours to forty-eight hours after inoculation, although fungi were seen in the glomeruli and inter-tubular vessels. The cellular reaction usually did not begin to appear until about the fourth day. They appeared first in the medulla and at this time the lesions were nearly all confined to the medulla. As they increased in size they became wedge shaped and spread to the cortex (fig. 2, *b*). Mycelium was never present in the lesions or capillaries although budding forms occurred (fig. 2, *d*).

The gross appearance of the lung was similar to that seen in animals inocuated with *M. albicans* but to a much less degree (fig. 1, *c*). The pleural surface showed a few subpleural hemorrhages and hemorrhagic areas on the cut surface in those animals on which autopsy was performed two to thirty-six hours after inoculation. The hemorrhagic areas were not present in animals seventy-two hours after injection. None of the rabbits in this group died of pulmonary embolism.

The microscopic examination of sections made from these lungs showed no mycelium in the tissues or associated with lesions but did show occasional budding forms. The alveolar capillaries appeared distended and serum and erythrocytes were seen in the alveolar spaces; eosinophilic leukocytes and lymphocytes and a few polymorphonuclear leukocytes formed aggregations of cells around the arterioles but the nodules seen in animals injected with *M. albicans* were rarely seen and Gram stains showed fungi which had lost their Gram reaction and appeared to be in process of disintegration.

DISCUSSION

The pathogenicity of an organism for one species of animal does not mean pathogenicity for all. And oppositely, the lack of disease producing attributes for one species does not mean non-pathogenicity for all. This has long been recognized and has

resulted in the selection of animals for individual tests. Thus white mice are used for the typing of pneumococci and guinea-pigs for the demonstration of tubercle bacilli; *B. mallei* is highly pathogenic for horses but is harmless for cattle. The results of animal experiments can not, therefore, be used to prove pathogenicity or non-pathogenicity for man, but they are useful in studying the mechanism by which tissue reactions are produced in those animals which react to them and in determining the relative virulence of different species of the same genus and different strains of the same species. Such studies are useful in establishing the identity of species by recognizing a constant difference in pathogenicity for the same animal or a characteristic histo-pathological reaction in the tissues.

In previous papers we have described a method of study by which we were able to classify under three species 150 strains of monilia isolated by us, and Type Cultures which were under a variety of species.

The animal work reported in this paper further emphasizes the significance of these three species. The dose required to kill rabbits, the clinical course of the animals, and the macrosopic and microscopic examination of tissues and organs removed at necropsy of animals injected with representative strains of organisms of each of the three species mark out sharply one from the other. *M. albicans* is revealed as the organism of greatest virulence and *M. parapsilosis* is shown to have no pathogenicity for rabbits, while *M. candida* in overwhelming doses, five to fifteen times greater than *M. albicans*, does produce occasional lesions in the kidney.

These results on the face of the gross and microscopic examinations of the tissue give the impression of a disease produced entirely by thrombosis and that the organism acts only in a mechanical manner by plugging the aterioles. Thus 8 per cent of the animals that died following injections of *M. albicans* died of pulmonary thrombosis, and the characteristic lesions were petechial hemorrhage in the lung and multiple abscess in the cortex of the kidney; all of which indicate a purely mechanical plugging of capillaries and arterioles.

On closer study, however, it is evident that the variability in the pathogenicity of these organisms is due to the difference in their ability to grow in the animal body and to invade the tissue. Microscopic examination of sections of lungs and kidneys removed two and four hours after inoculation shows an early degeneration of *M. parapsilosis* evidenced by its appearance in the capillaries as Gram positive bodies which were beginning to break up. They never produced mycelium in the animal body although it is an abundant mycelium producer in certain culture media. This organism has not manifested any evidence that it has the ability to reproduce in the blood stream. In spite of the fact that it was administered in doses two hundred times larger than the doses of *M. albicans*, it produced no lesions and sections stained with Gram's stain revealed very few fungus cells in the capillaries and many of these were degenerated forms.

On the other hand, *M. albicans* manifested evidence of vigorous and rapid multiplication in the blood stream. The sections of lungs and kidneys, removed at two and four hours (fig. 2, *e*), showed many Gram positive fungus cells, many budding forms and strands of mycelium in the capillaries of the alveolar walls and glomeruli. As the disease process progressed the mycelium became more abundant (fig. 2, *f* and *g*).

By this same kind of evidence *M. candida* showed only feeble powers of multiplication in the blood stream. In sections of lungs and kidneys removed at two and four hours the Gram stain revealed Gram positive fungus cells, a few of which were beginning to lose their Gram reaction.

With this manifestation on the part of *M. albicans* to multiply vigorously in the blood stream, we, of course, expected that while mycelium production would cause mechanical occlusion of some of the arterioles it should also invade tissue. This invasion would be accomplished, if by no other method, by breaking through structures due to rapid increase in the number of fungus cells. With this idea in mind we performed local injections into the nasal accessory sinus, subcutaneous, intramuscular, intrapleural injections and directly into the kidney.

The subcutaneous inoculations resulted in abscesses which

healed in about ten to twelve weeks. The direct inoculation in the left kidney resulted in septicemia with local lesions occurring in the opposite kidney and the brain (figs. 1, *b*). The intramuscular injections resulted in lesions in the kidneys and the inoculations into the nasal sinuses caused miliary moniliasis. *M. parapsilosis* and *M. candida* produced neither local nor general reactions by this method of administration. These experiments give evidence of the invasive power of *M. albicans* as well as its ability to reproduce in the tissue, and the inability of either *M. parapsilosis* or *M. candida* to invade tissue.

TABLE 4

SIZE OF FUNGUS CELLS IN EACH TYPE

TYPE	CULTURE NUMBER	LARGEST	SMALLEST	AVERAGE	TOTAL AVERAGE
		micra	*micra*	*micra*	*micra*
I	50858	7.1	2.1	4.5	
	35221	7.1	2.1	4.73	4.63
	38746	6.0	3.2	4.65	
II	4135	12.0	2.8	6.1	
	801	9.7	2.4	6.0	6.03
	33691	9.5	3.1	6.0	
III	750	9.9	3.4	6.4	
	14999	8.7	4.2	6.43	6.37
	23669	11.0	3.0	6.29	

One criticism that may be offered is that the doses were extremely large and that the conditions are, therefore, highly artificial. This objection may be offered to many animal experimentations. No animal experiments ever reproduce the circumstances and environment of infection in man. That the size of the dose was not the determining factor was illustrated in these experiments by the fact that the organisms which showed no or but little pathogenic properties were the very organisms which were administered in doses of two hundred to a thousand times larger than those which demonstrated these characteristics.

We were further concerned about the mechanical factor involved in the pathogenicity of these organisms. If the results were

due only to mechanical occlusion of arterioles and capillaries, it seemed reasonable that the species which was most constant in its production of lesions when administered in relatively small doses would be much greater in physical size. We, therefore, grew three cultures of each species for forty-eight hours on malt agar and suspended the growth in normal saline. The size of the cells in the suspension was determined by measuring 100 cells in each suspension. Table 4 shows the results.

It is seen from this table that *M. parapsilosis* is the smallest organism and it also is not pathogenic; but, on the other hand, *M. candida*, which shows only feeble ability to grow in the animal body and to produce lesions has an average size somewhat larger than *M. albicans*. The variability in size of the different species does not reveal enough difference to explain their difference in pathogenicity.

To examine still further the idea of plugging of arterioles and capillaries, when the factor of reproduction in the blood stream or tissue was eliminated, we prepared suspensions in normal saline of cultures of *M. albicans* and *M. candida* to which was added enough formaldehyde to make a 0.5 of 1 per cent solution. When the organisms were dead, proven by culture, rabbits were inoculated with doses of each which had previously either killed the animal or produced numerous lesions. No animal showed any sign of illness following these injections and gross and microscopic examination revealed no vascular obstruction.

CONCLUSION

We believe that these experiments have revealed a fundamental difference in pathogenicity for rabbits, for the three species of monilia used in these experiments; that the postmortem examination four hours after inoculation of rabbits given intravenous doses as described in this paper reveals characteristic differences for the three species of monilia used, and that simple mechanical occlusion of arterioles and capillaries does not explain the nature of the pathogenicity, but that ability or failure to grow in the animal body and invade tissue has been demonstrated to be the principal quality accountable for the decided virulence of *M. albicans*,

the feebly pathogenic properties of *M. candida* and the lack of this characteristic in the case of *M. parapsilosis*.

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MONILIASIS OF THE LUNGS AND STOMACH

Case Report with Autopsy*

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One finds in the literature a good many references to the isolation of monilia or yeast-like organisms from the sputum. A few of the reports describe clinical conditions of either mild or severe pulmonary moniliasis. But undoubtedly in many instances the finding of monilia in the sputum indicates only, that these organisms are at most secondary invaders. Some authors report fatal cases attributed to infection of the lung with monilia.

In 1924, Johns[1] reported five cases of moniliasis, and mentioned the work of Castellani, who, in 1905, described the condition in Ceylon. Johns stated also that only two cases had been reported in this country previous to his own. For complete information concerning the subject, including the historical references in the literature, clinical and experimental data, and data for identification and classification of the monilia, one should consult the following authors in addition to those mentioned above: Stovall and Greely,[6] Stovall and Bubolz[3, 4, 5] and Stokes and Kiser.[2]

A limited survey of the literature does not reveal any necropsy report linking up the clinical diagnosis of pulmonary moniliasis with pathological findings in the lung. Stovall and Greely[6] mentioned having isolated monilia from autopsy material in one case. Therefore the following case history with pathological data is presented. No attempt is made to enter into a complete description of any phase of the report, especially the cultural or animal studies made with the organism isolated.

* Read before the Twelfth Annual Convention of the American Society of Clinical Pathologists, Milwaukee, Wisconsin, June 9–12, 1933.

CASE REPORT

Mrs. B., aged fifty years, white, with a feeling of well being and "don't care" attitude not in keeping with her physical appearance, only after much prompting, stated that for the past two years she had suffered from "indigestion," cough with expectoration, a pain in the back between the shoulder blades, and loose bowels, two to six movements a day, with exacerbations. In fact it was quite difficult to get her to admit that she was ill in any way.

Physical examination presented a fairly well developed, but very emaciated, white female, with a slightly yellow color, wrinkled skin, atrophic and inelastic tissues. The knee jerks were markedly diminished, pupils were equal and reacted to light. There were no enlarged nodes. She presented glistening sclera, artificial denture, a smooth red, glazed tongue, and the entire pharynx was markedly pale and anemic. The tonsils were atrophic and contained sero-pus. The thyroid was small. The thorax presented bony fixation, hyperresonance in the uppers and considerable impairment of resonance over the left base posteriorly, with diminution in breath sounds, sonorous, sibilant and crepitant râles, generally scattered over the chest but more marked over the bases, particularly the left. The heart was not enlarged; there was no increase in the upper mediastinal dullness, no murmurs, no arrhythmia, and no change in sounds. Her blood pressure was 110 systolic, 70 diastolic. The abdomen tympanitic throughout. The spleen was not palpable. There was considerable tenderness over the region of the gall bladder, liver, and pylorus. Vaginal examination revealed an atrophic uterus, ovaries, and cervix, without other evidence of disease. The rectum presented a number of tags and varicose veins. Extremities showed no disturbance in sensation. There were numerous pigmented scars on both legs, due to ulcers many years before. The temperature ranged from 99° to 102°, pulse from 100 to 130. The patient coughed a great deal and brought up daily several ounces of light greenish, thick, creamy sputum.

Radiographic examination of the chest showed an elevation and partial fixation of the left diaphragm, which was rendered more or less obscure by the pathology at the base of this lung. The cardiac and great vessels were not enlarged; the right pulmonic field presented numerous dilated bronchioles and bronchiectatic changes at the base, while the left pulmonic field showed well defined areas of consolidation in the lower lobe. The upper half of the fields were free from infiltrative processes and showed extensive bronchial dilatation with fibrosis, presenting a general honey-comb appearance over the entire area. The radiologist's conclusions were: Chronic broncho-pneumonia, bronchiectasis, and purulent bronchitis.

The urine showed a few pus cells and erythrocytes, a few hyaline and fine granular casts. The stool was brown, semi-solid, many Strongyloides larvae present, no amebae, no monilia in smears; cultures were not made. The gastric contents contained no free HCl even after histamine, but many pus cells, monilia, other organisms and occult blood. Many examinations revealed a thick,

creamy, light green sputum, with a musty odor, and consisting of mucus, elastic tissue, large numbers of monilia, and a few other organisms; no blood was seen. Occasionally the monilia were scarce, or absent in smears, but by incubating the sputum itself, or making cultures, monilia were always found. Often specimens examined immediately after expectoration revealed enormous numbers of monilia. Acid-fast bacilli were never found in the sputum.

Wassermann, Kahn, and slide precipitation tests were negative, and the spinal fluid was normal. Many examinations of the blood revealed a pernicious-like type. On admission: erythrocytes, 2,515,000, hemoglobin, 11.5 grams or 81 per cent, color index, 1.57 volume index, 1.35, reticulocytes, 2 per cent, blood platelets, decreased, moderate anisocytosis and poikilocytosis, slight polychromatophilia and stippling, and a rare nucleated erythrocyte. Van den Berg, direct negative, indirect two units. Slight trace of urobilinogen in urine.

It was therefore concluded that the patient was suffering from pernicious anemia, monilia infection of the lungs and stomach, and a chronically diseased gall bladder and appendix, with degenerative changes in the liver, and a mild nephritis. She was placed on large doses of potassium iodide by mouth, dilute hydrochloric acid, a diet of fresh foods, liver, and liver extract by mouth. Blood transfusion and iron were also tried. With only temporary improvement shown in the midst of her illness, she died after five months of observation and treatment.

Guinea-pigs inoculated with the sputum treated with antiformin never showed any evidence of tuberculous infection. Inoculation of untreated sputum produced local abscesses in guinea-pigs. Most of the pigs inoculated intraperitoneally, intrapleurally, and into the liver, developed monilia lesions. Certain pigs died in three or four days, some in ten to fourteen days, and others survived. The culture is still pathogenic for guinea-pigs, though it does not produce death so quickly as before, or so frequently. The lesions produced are abscesses or pseudo-tubercles, which undergo fibrosis to a great extent. In the lungs of the animal there is produced the same type of reaction.

The organism is oval shaped, from 3 to 10 microns in diameter, is gram positive, and produces rarely a few short branches or hyphae on media. Acid and gas developed in glucose, levulose, mannose, maltose, galactose, and acid only in sucrose. There was no reaction in lactose, inulin, raffinose, dextrin, gelatin, or litmus milk. There were no mycelial colonies on malt agar at the end of forty-eight hours.

The monilia (albicans) in question would fall into type II, of Stovall and Bulbolz.

Autopsy report

External examination. The body is that of a white female, aged about fifty-years, and is extremely emaciated. The skin is dark, cyanotic, or brownish colored. The tongue is generally reddened and the papillae atrophic. The anterior surfaces of both legs are covered with large dark pigmented scars or patches.

Internal examination. Abdomen: The little subcutaneous fat remaining is somewhat yellowish. The liver is not enlarged, and presents a nutmeg appearance with much fatty degeneration. The gall bladder is covered with old adhesions, is thick and white, but stones are not present. On handling the stomach and breaking up adhesions it is torn at the pylorus, which is seen to be the site

FIG. 1. SMEARS FROM PYLORIC ULCERS SHOWING MONILIA

of a large ulcer which has almost perforated the organ. On opening the stomach the mucosa is found to be eroded and atrophic, and presents numerous petechial hemorrhages. Near the pylorus the mucosa is especially atrophic, and four ulcers are seen, one above and one below the ring, and two at the ring, one of which had been ruptured by handling. These ulcers are filled with a yellowish, greenish, thick, creamy exudate. Smears later revealed many monilia, almost

always without other organisms. The spleen is considerably enlarged, the capsule strips easily. The cut surface is reddish brown, the pulp comes away easily, revealing a good deal of fibrosis. The kidneys are slightly enlarged, capsule strips easily, revealing a reddened surface, the blood vessels in the cortex being very prominent.

Thoracic cavity: There is no fluid present, the pleura is freed from the thoracic cage and diaphragm with great difficulty, and is about 3 mm. in thickness over a great part of both lungs, which show about the same pathology, the left being more involved. The apices are practically free of pathology. On cutting into the lung a remarkable picture is presented, a greater part of both lungs being

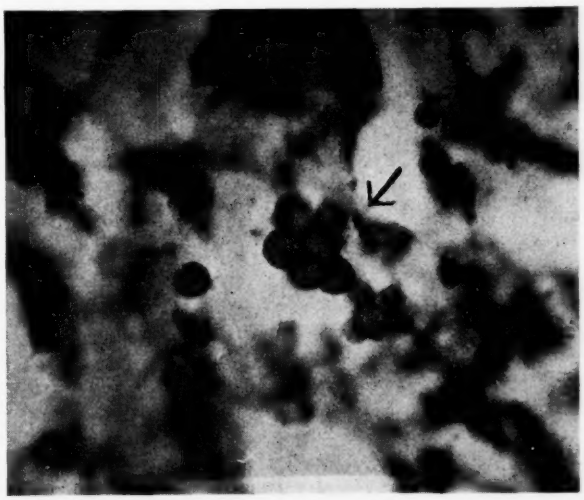

FIG. 2. LUNG OPENED TO SHOW LESIONS

Note multiple cavities throughout associated with bronchial passages. They were filled with greenish pus.

involved. Superficial lung tissue is fairly normal and crepitant. The lung (fig. 1) is honey-combed with countless small pus pockets, ranging from 3 mm. to 2 cm. in diameter. These pus pockets are mostly associated with the medium-sized and small bronchioles, but also involve the adjacent lung tissue. The pus is light greenish in color, smears later revealing monilia in almost a pure state. Very little normal lung tissue remains, as the areas not showing pus are mostly very dense or fibrous. It is difficult to understand how the patient existed so long with so little normal lung tissue.

The heart is not enlarged, the pericardium is slightly thickened, and the myocardium is somewhat brownish and fibrous. There is no evidence of valvula disease. The aorta shows a few arterio-sclerotic plaques.

Bone marrow of the femur shows a red hyperplastic condition grossly. Smears revealed a very active bone marrow, such as is seen in pernicious anemia. Prussian blue reactions were obtained with tissue from the spleen, kidney, and liver.

Microscopic examination of the lungs: There are several types of lesions present, depending upon the stage of the process. (a) Pseudo-tubercles consisting of a central area of pus cells and mononuclear cells, then fibroblasts, epitheloid cells, plasma cells, and young blood vessels; monilia are scattered throughout (fig. 2). There are very few giant-cells and these are not typical. (b) Fibrosis or granulation tissue (fig. 3) in various stages, with aggregations of small round

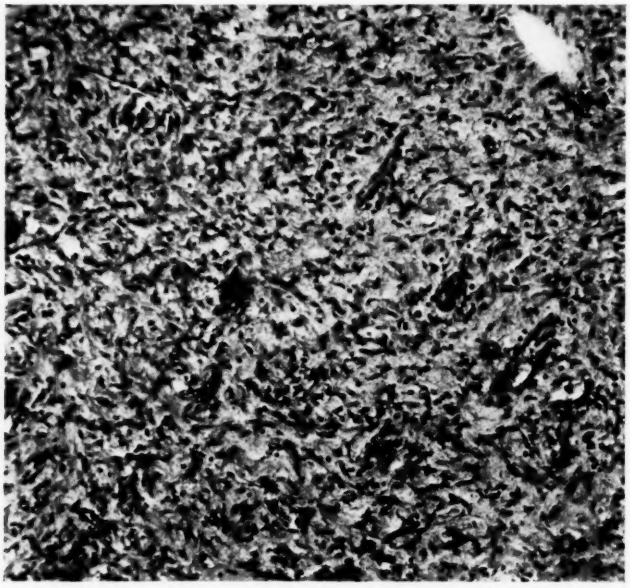

FIG. 3. SECTION OF LUNG

cells and plasma cells. (c) Around the bronchioles of various sizes are chronic inflammatory changes with much fibrosis. Adjacent lung tissue shows a diffuse fibrosis or chronic lobular pneumonitis. Very few areas show lung tissue without chronic inflammatory changes. There is a marked tendency for healing of the pseudo-tubercles by fibrosis, except the bronchiectic areas. Calcification was not found. Areas like that seen in tuberculous infection were not found.

Sections of the stomach ulcers present an ordinary ulcerative type of reaction superficially, and deeper chronic inflammatory changes. Some of these areas present granulation tissue similar almost to sarcoma.

Sections of the liver show a diffuse hepatitis of a fatty and parenchymatous

degenerative nature, with deposits of blood pigment, and some cirrhosis and congestion.

Sections of spleen show passive congestion, pigmentation, and fibrosis.

Sections of the gall bladder show marked chronic cholecystitis.

Sections of the heart show parenchymatous degeneration, fibrosis, and some pigmentation.

COMMENT

The patient presented clinical and pathological evidence of a severe late moniliasis of the lungs and stomach, in addition to the picture of pernicious anemia. The blood picture, absence of free HCl after histamine, and the pathological findings necessitate the diagnosis of pernicious anemia in addition to that of moniliasis, though the slight trace of urobilinogen in the urine, and only moderate increase in the van den Berg reaction is not the usual finding in pernicious anemia. Then too, the condition of the patient's blood did not improve a great deal under adequate liver therapy. This might be explained by the severe accompanying moniliasis, and perhaps lack of a potent liver extract to administer. On the other hand the pernicious-like anemia might be attributed to moniliasis of the lungs and stomach.

It would have been interesting to have made roentgengrams later in the disease to show progress of the lesions. Intravenous iodides, copper, gentian violet, or autogenous vaccines might have been tried, but on the whole, I believe the disease was too far advanced for any method of treatment to have benefited the patient. No agglutination tests with the patient's or with animal's serum were made. Blood cultures were not made.

SUMMARY

(1) A fatal case of pulmonary and gastric (pyloric) moniliasis accompanying a pernicious-like anemia is presented with fairly complete antemortem and postmortem data.

(2) The patient presented clinically a picture similar to that of advanced pulmonary tuberculosis.

(3) The copius sputum contained large numbers of *Monilia albicans*, type II (Stovall). The monilia isolated is rather pathogenic for guinea pigs (other animals not used), even after more than two years of artificial cultivation.

(4) Iodides by mouth did not stop the progress of the disease, perhaps due to the late extensive involvement when treatment was begun.

(5) More frequent study of sputa is indicated for the purpose of detecting monilia and other fungi infections of the lungs.

(6) Monilia in sputum is a rather frequent finding, and is perhaps more often a nonpathogenic secondary invader.

(7) The finding of monilia should not prevent a further search for other causes of pulmonary pathology.

The author wishes to acknowledge the aid and coöperation rendered by Drs. H. J. Mixson, F. Y. Durrance, and J. D. Blevins and Carolyn Van Zandt, the latter superintendent of the Jefferson County Tuberculosis Hospital. Also I am indebted to Dr. W. D. Stovall for his cultural studies in confirming my exact identification of the monilia organism described.

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NEW METHOD OF RETICULOCYTE ENUMERATION

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A new method of reticulocyte enumeration is proposed on the premise that it is a rapid and accurate procedure.

The staining solutions and technique employed in making the blood preparation for study are as follows:

Solution A

Neutral potassium oxalate	1.0	gram
Sodium chloride C.P.	0.85	gram
Distilled water	100	cc.

Solution B

Brilliant cresyl blue	1.0	gram
Sodium chloride C.P.	0.85	gram
Distilled water	100	cc.
Chloretone (as a preservative)	1.0	gram

In a conical tipped centrifuge tube place 25 parts of solution A and 5 parts of solution B, mix,* and add several drops of blood. After thoroughly mixing, permit to stand 10 to 20 minutes, then centrifugalize for 20 to 30 seconds at a moderate speed. The supernatant fluid is pipetted off until a layer of fluid approximately equal to the depth of the sediment remains. Mix the sediment well with the supernatant liquid, draw up in the pipette and discharge one drop near the end of a perfectly clean glass slide.

Spread the stained drop with the edge of a coverslip square 18 mm. and draw the film to about 6 cm. from the starting point. The characteristic graded film prepared in this way appears as illustrated in figure 1 when dry and ready for study. The underlying principle of the method involves the Relative Reticulocyte Distribution (R.R.D.) throughout the smear. To know the relative distribution of reticulocytes is important, since it is technically not possible to make a blood film manually so that the distribution of erythrocytes and reticulocytes is equal throughout the preparation. It has been determined, however, that the distribution varies in a definite way when the above technic of preparing smears is followed each time.

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* Since a precipitate forms when the solutions are mixed, it is better to make up a larger volume, filter and place the proper amount of the mixed solution in the tube and proceed.

Technic of reticulocyte count

The R.R.D. is found as follows: Divide a piece of paper into 10 columns and mark them 1 to 10. Adjust a 4x eyepiece to a tube-length of 190 mm., using an oil immersion objective 1.8 mm. × 95 N.A. 1.30 in order to obtain the specific microscopic working field. Any other combination giving the same field may be used.

The R.R.D. in the film will usually be found to show about four variations in concentrations as follows: (1) extremely high, (2) high, (3) low, (4) extremely low or absent.

Place the objective on the upper edge of the film near the starting point, that is the extreme left border of the film (See fig. 1). Moving the slide upwards in a vertical line, count several fields that show the highest as well as the moderately high, moderately low and low reticulocyte concentrations. Record the counts of each classification in column 1. When the lower edge of the film is reached, move the slide to the left horizontally 0.5 cm. (measured by the mechanical stage) from this point move the slide downward, count the reticulocyte concentrations as before and record them in column 2. Count ten vertical zones in this manner. If a vertical zone does not show any reticulocyte, mark in the corresponding column a zero.

In a vertical zone 18 mm. in length there will be found approximately 150 microscopic fields, the average field showing about forty erythrocytes. There should be counted and recorded in each column the number of reticulocyte concentrations found in at least eight to ten fields in each vertical 18 mm. zone. Select (for example see table 1), from the 80 to 100 individual enumerations recorded in the ten columns ten reticulocyte counts distributed as follows:

(a) Two fields showing extremely high concentrations.
(b) Three fields showing high concentrations.
(c) Two fields showing low concentrations.
(d) Three fields showing extremely low to absent concentrations.*

Having added the ten reticulocyte counts the total number is referred to as the sum of reticulocytes (S_R). In the same ten fields there are 400 erythrocytes. The ratio of reticulocytes to erythrocytes (for example see table 2) is therefore,

$$\frac{S_R}{400}$$

The percentage of reticulocytes is

$$\frac{S_R}{400} \times 100$$

or

$$\text{per cent} = S_R \times .25$$

* When selecting the individual reticulocyte counts use as many zeros as there have been zero columns. (See table 2.)

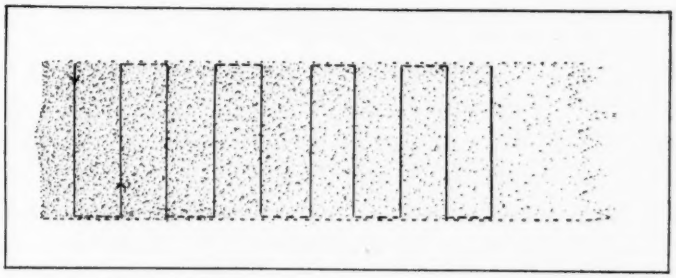

FIG. 1. METHOD OF COUNTING RETICULOCYTES

TABLE 1

EXAMPLE OF METHOD OF RECORDING RETICULOCYTE COUNTS

COLUMNS									
1	2	3	4	5	6	7	8	9	10
12	10	10	9	6	4	4	7	2	2
7	15	12	6	5	5	2	8	1	**2**
9	**10**	6	6	10	8	4	3	2	3
18	9	12	**8**	5	12	**6**	8	**4**	1
12	6	5	8	3	6	4	5	3	**1**
12	6	14	4	5	4	6	5	4	1
16	12	10	10	4	4	8	7	5	2
7	**14**	8	10	7	4	5	4	4	1
15	8	7	4	10	4	6	3	5	3
9	4	9	9	6	5	4	2	2	2

TABLE 2

EXAMPLES OF CALCULATING RESULTS OF RETICULOCYTE COUNTS

A*	B	C	D
18	8	2	3
16	5	2	2
15	4	1	1
14	3	1	1
10	3	1	1
8	2	1	1
6	2	0	1
4	1	0	0
2	1	0	0
1	1	0	0
$S_R - 94 \times .25 =$ 23.2 per cent	$S_R - 30 \times .25 =$ 7.5 per cent	$S_R - 8 \times .25 =$ 2.0 per cent	$S_R - 10 \times .25 =$ 2.5 per cent

* The counts recorded in this column are taken from table 1, columns 1, 2, 4, 7, 9 and 10 in accordance with the method described above for selecting individual reticulocyte counts on the basis of relative reticulocyte distribution.

COMMENT

This method of calculating a reticulocyte percentage is rapid and accurate. The method eliminates the enumeration of erythrocytes. It requires only ordinary apparatus and any observer recounting the same film is able to arrive at practically the same result on each enumeration. The limits of error of the method herein described are ±1 per cent, showing a much lower technical error than other methods. Low concentrations as well as high concentrations of reticulocytes are readily calculated.

From the careful studies of several hundred smears made from normal human blood showing balanced red blood cell and hemoglobin concentrations by this method, I have established that the normal range of reticulocyte concentration is 2 to 3 per cent, with an average of 2.5 per cent.

The author acknowledges with thanks the interest shown by Dr. E. A. Sharp, Director of the Department of Experimental Medicine, and Dr. E. P. Bugbee, Research Physiologist, Parke, Davis and Company.

A CULTURE MEDIUM FOR RAPID GROWTH OF PASTEURELLA TULARENSIS

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A pressing need for large amounts of dense suspensions of *P. tularensis* has resulted in the formulation of a new modification of Francis'[1] original cystine-dextrose agar. A medium was wanted that could be prepared quickly and that would support a rapid and abundant growth of this fastidious and rather delicately growing organism. After many trials the present medium was adopted as the most satisfactory one in these respects, and during the past two years its routine use has simplified the matter of obtaining a large quantity of antigen.

PREPARATION OF THE MEDIUM

Twenty-four grams of "Difco" dehydrated brain-veal agar and 2 grams of nutrose are dissolved with gentle heat in one liter of distilled water containing 5 grams NaCl, 0.3 gram Na_2HPO_4, 0.2 gram KCl and 0.1 gram $CaCl_2$. The mixture is divided equally among four 500 cc. flasks and set in the refrigerator to solidify. After solidification 0.1 gram of cystine is placed in a small pile on the center of each surface. If care is taken not to stir the cystine around the medium may be autoclaved safely at fifteen pounds for fifteen minutes without impairing the growth-promoting property of the cystine. Upon removal from the autoclave the flasks are set in a row and each is rotated vigorously in turn until the sedimented cystine is dissolved. This usually requires about ten minutes.

If only 250 cc. of enriched medium is desired, three flasks are capped and put in cold storage and one is cooled to about 50°C. To this flask is added 10 cc. of 25 per cent dextrose and 30 cc. of either ascitic fluid or any sterile serum diluted 1:5. The contents are well mixed, then tubed and slanted or used to fill Blake bottles. Other flasks are melted and enriched similarly as needed. Slanted tubes are capped as soon as set to prevent water loss. If a liter of finished medium is wanted the base medium may be solidified in one large flask, 0.35 gram of cystine added, autoclaved, cooled and enriched with 40 cc. of 25 per cent dextrose and 120 cc. of ascitic fluid or diluted serum.

COMMENT

The medium is characterized by a low agar content with a rubbery, resilient surface which facilitates rapid inoculations and washing and minimizes the chances for ploughing up medium into the bacterial suspensions. This combination of low agar content, maximum hydration with but little free water, and a good working surface is made possible by the inclusion of nutrose.

P. tularensis will grow rapidly and luxuriantly on the surface but not in the water of syneresis. The seventy-two hour growth from three Blake bottles will yield about 50 cc. of a washed suspension of 5,000 turbidity. Growth on slants is best at partial oxygen tension and, because of the tendency of the slants to slump when warmed, they are incubated in a slanting position. Partial oxygen tension is obtained by the tandem arrangement devised by Wherry and Oliver.[2] Although *P. tularensis* is described as aerobic it is more properly a microaerophilic or partial tension organism. On all mediums on which I have been able to grow it the growth has invariably been faster and more abundant at partial oxygen tension than under aerobic conditions.

The medium is not good for preservation. Cultures will usually not remain viable, as judged by subculturing, for more than eight days. Strains that are being carried along on it are best transferred twice a week. For isolation of *P. tularensis* from infected rodent tissues it is only fairly good, inferior to blood-cystine-dextrose agar and to coagulated egg yolk. Its chief virtues are its capacity to promote rapid and abundant growth, and the short time and ease of making. The base medium can be stored indefinitely at low temperature, and tubes of the enriched medium are good for at least three months if water loss is prevented.

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THREE NOTES ON BIOLOGICAL STAINS

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1. COMBINED PEROXIDASE-WRIGHT'S STAIN FOR BLOOD FILMS

I have been using since 1928 a combined peroxidase-Wright's stain procedure which seems technically superior to Washburn's[3] method in that the basic fuchsin has been omitted from the oxydase reagent, eliminating the decolorizing step of his procedure, and in that prolonged staining periods are not required. It is not necessary to stain the film within a few hours after its preparation. I have obtained perfect stains on films which have stood as long as forty-eight hours at room temperature.

The oxydase reagent consists of 0.3 gram of pure benzedine base dissolved in 100 cc. of 95 per cent ethyl alcohol to which is subsequently added 1.0 cc. of a saturated aqueous solution of sodium nitroprusside. It keeps well, but should be made up freshly about once every six or eight months. The blood film is flooded with this reagent which is allowed to act for one minute.

The secret of success in peroxidasing the film lies in securing the proper concentration of hydrogen dioxide in the subsequent treatment. The traditional concentration of 1:200 made by adding three drops of a 3 per cent hydrogen peroxide solution to 15 cc. of water is probably nearly perfect, but the instability of the commercial reagents renders it difficult to be certain of exactly this proportion. In preparing to peroxidase a leukemic blood I run a number of films from normal controls through a series of four or five different hydrogen peroxide dilutions, using the standardized time factors given below, in order to determine which is most suitable. If this is done it will be found that as the concentration of hydrogen dioxide increases the jet black peroxidase granules in the finished stain first become more minute and discreet and subsequently turn to a greenish brown in color, finally

from too strong peroxide concentrations disappearing altogether, due apparently to the bleaching action of the reagent. This fact can be further demonstrated by dropping a strong peroxide dilution upon the center of the film flooded with the oxydase reagent, allowing it to spread to the edges by diffusion, when it will be found that the most perfectly stained granulocytes lie on the edges of the film, those in the center showing the greenish brown coloration. When the proper dilution of hydrogen peroxide is determined, without pouring off the oxydase reagent, add a little less than half of the amount of this reagent used. Drop the peroxide dilution onto the flooded film at the ends of the slide and endeavor to secure uniform diffusion by blowing on the surface of the liquids or tilting the slide slightly back and forth. Let the combined reagents act for not longer than two minutes.

The success of the counterstain by Wright's stain upon the peroxidased film depends upon controlling the ion concentrations. The peroxidasing procedure tends toward acidifying the film which results in accentuated reds by Wright's technic and depression of the blue staining. The film is therefore best washed thoroughly after pouring off the oxydasing solution in running tap water which is slightly alkaline (pH 8.0–8.2) for a full minute and allowed to dry in air. The drying may be hastened by blotting or under an electric fan, the latter being preferable.

The film is next stained by Wright's method in the usual way. All bloods after the peroxidasing treatment require slightly longer staining periods but I have not found that leucemic bloods require any longer staining than normals.

The time factors for the various steps which I have found most suitable are: for peroxidasing, one minute by oxydase reagent followed by two minutes after the addition of the hydrogen dioxide solution. For Wright's staining after washing and drying, three minutes by the stain followed by five minutes after the addition of the water.

2. AN ORANGE-BROWN GRAM COUNTERSTAIN

Basic fuchsin and safranin are unquestionably the most practical aniline dyes for use as Gram counterstains in a routine

laboratory, due to the ease of preparation of the stain from stock solutions which keep indefinitely. Where large numbers of slides are being examined continuously, as in the microscopic examination of routine throat cultures made on every patient admitted to a hospital, the red color of Gram negative organisms eventually becomes tiring to the eyes. Bismarck brown, which was at one time strongly recommended as a counterstain and then fell into disuse through the instability of its solutions, has come to the fore again since Huntoon[1] has shown how to make staining reagents of good keeping qualities from this dye by the inclusion of 25 to 30 per cent of glycerine in the formulas. Bismarck brown gives a rather dark brown to Gram negative organisms which often does not contrast well with the Gram positive color. The following formula has been found to keep indefinitely and to give a rich orange-brown color that is both more restful to the eyes than fuchsin or safranin alone and contrasts strongly with the Gram positive blue:

Shake up 1 gram of Bismarck brown in a flask with 100 cc. of 25 per cent aqueous glycerine. Add 1 cc. of stock saturated alcoholic basic fuchsin or safranin and let stand with occasional shaking at room temperature for a day or two. Filter into the dropping bottle.

3. A STABLE PAPPENHEIM PYRONIN-METHYL GREEN STAIN

Two new dyes have recently been placed on the market by National Analine and Chemical Co., Inc., which they have developed in co-operation with S. A. Scudder[2] and the Commission on Standardization of Biological Stains, especially for use in Pappenheim's stain. They are known as pyronin, "yellowish," which corresponds more closely to the pyronin "gelb," of German manufacture than any other heretofore produced in this country, and methyl green-national, which is an over ethylated product especially recommended for use in the Pappenheim stain. In ordering the latter it is necessary to specify certification number subsequent to NG 7, with which lot the new formula went into routine production.

For those who prefer the color differentiation of the Pappenheim stain either as a histologic stain or as a Gram counterstain these

new dyes will represent a distinct advance. At the time of presentation of her paper Scudder had not found any means of stabilizing the Pappenheim formula so as to avoid the necessity of making up a fresh lot of stain each time that it was desired to use it. I have tried the effect of 25 per cent of glycerine as suggested by Huntoon's work and found it entirely successful. Made up in this way the stain has remained apparently unaltered in its staining characteristics for over seven months. It may be prepared according to Scudder's formula:

Pyronin, yellowish	0.1 gm.
Overethylated methyl green	1.25 gm.
Hot 25 per cent glycerine in distilled water	99 cc.

Or two stock solutions of 2 per cent methyl green and 0.3 per cent pyronin, yellowish, can be made up in 25 per cent glycerine and mixed, in various proportions, according to the individual taste, light, and character of work.

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EDITORIAL

The Importance of Celsus to Modern Medicine and Pathology

It will be a source of satisfaction to physicians generally to know that the Loeb Classical Library has in preparation a new English translation of the Eight Books of Celsus on Medicine. During the century from 1750 to 1850 it was the practice abroad "to prescribe Celsus as one of the tests by which the candidate is to be tried." Alex. Lee in the preface to his admirable English translation of 1831 gives the reason why Celsus should be taught in all medical curricula:

> Even where our author is evidently wrong, for instance in his anatomical descriptions, I have preferred to err with him, rather than be right against him: for this very reason, that the student may see Celsus as the faithful representative of medical science in his age, and contrast that with the present improvements.

As Aurelius Cornelius Celsus lived from 25 B.C. to 50 A.D., he was contemporary with the beginning of the Christian era. If Celsus had been taught continuously, our medical students would always have had a "point of departure" with which to compare current medicine.

If medical students from the time of Thomas Sydenham had been required to know the medicine of Augustan Rome, there would not have been so many discoveries in therapeutics, dietetics, internal medicine and surgery as has been the case, for Celsus was well aware of many of the things in medicine and pathology which we attribute to a very much later age. Largely because he wrote books on other subjects as, for instance, agriculture, military science, et cetera, it was supposed that he was not a practitioner of medicine. It would seem to be about as reasonable to contend that he was not an active practitioner on this basis, as to argue that S. Wier Mitchell was not a doctor because he was also an authority on snakes. If Celsus did not practice

medicine in Rome, then the Romans certainly lost a great man in the healing art.

During the middle ages Celsus' works on medicine were completely lost sight of. In 1443 Thomas of Sarzanne, who was later Pope Nicholas V discovered the manuscript of the "De Re Medicina" in Milan and in 1478 it was printed. Between that date and 1769 editions of Celsus appeared in Latin and apparently there was some disagreement in these texts as to exactly what the author meant in many cases. In the year 1769 the edition of Targa came out and from that date there has been little disagreement regarding the author's meaning as this work seemed to have settled most of the discussions on this matter. For about a hundred years after this date most editions of Celsus were printed in Latin.

In the 18th and early 19th centuries several translations were made into English and one or two into French. The English translations have all been out of print for many years. At the present time there are five or six of these translations which are admirable, but these books can only be found in rare libraries or in old book shops in England or on the continent. A few of these editions will be enumerated here.

(1) Edition of James Greive, 1756, went through several editions; the third edition is dated 1814. There is a copy of this work in the Columbia University Library, New York, in the Kings County Medical Society Library, Brooklyn, and in the Surgeon General's Library in Washington.

(2) The edition of Alex. Lee which is a translation of Targa's Celsus from the Latin of 1769. This is an admirable translation; two volumes bound in one with the Latin of Celsus and an ordo verborŭm, the purpose of which was to aid those students who were not familiar with classical Latin. This edition has an excellent English translation and wonderful notes on the entire eight books with a complete index, an index of the authors quoted, the life of Celsus, et cetera. This most excellent edition of the works of Celsus was published between 1831 and 1836. There is a copy of this in the Surgeon General's Library, the Kings County Medical Society Library and in the Library of Congress. It is rare.

(3) The Works of Celsus adopted for Students of Medicine by J. W. Underwood, 1830. This work is in two volumes and the translation is on the interlinear plan which gives the volumes a very ragged and difficult appearance and, I should think, would not have been popular with the students of those days when the translation was made (1829 to 1833). Copies of this edition are to be

found in the Harvard College Library and in the Kings County Medical Society Library.

(4) The First Four Books of A. Cornelius Celsus De Re Medica, with an Ordo Verborum and literal translation by John Steggall. This is the least satisfactory of the several English translations I have seen. The second edition of this work was published in London in 1843. There is a copy of it in the Kings County Medical Society Library.

(5) One of the most satisfactory renderings of the Works of Celsus is that translated into French in 1876—Traité De Médicine De A. C. Celse. Traduction nouvelle, avec texte latin, notes, commentaires, tables éxplicatives, figures dans le texte, et quatorze planches contenant, 110 figures d'instruments de chirurgie antique, trouvés dans fouilles de villes Gallo-Romaines, de Pompii et d'Herculanum; Par Le Dr. A. Védrènes, Médicin Principal de l'Armee, chevalier de la Légion d'Honneur, de l'ordre de Pie IX, precédé d'une préface par Paul Broca. Professeur a la Faculté de Medicine de Paris, Membre de l'Académie de Médicine. Paris: G. Masson, Editeur Libraire de l'Académie de Médicine, Place de l'ecole de Medicine MDCCCLXXVI.

(6) Lastly, there are the several editions of the translation of G. F. Collier. The third edition of this translation came out in 1838. It is a very good edition of the work and is fairly common in the old book shops abroad. It has only the English text of the translation. The third edition is a duodecimo volume of about 370 pages and has some twelve or fourteen illustrations.

(7) All of the above mentioned translations are in the library of the New York Academy of Medicine.

Some of the expressions of Celsus are as fresh and frank as one could wish from a medical scientist. Take for instance, the opening paragraph of the section on "Diseases Incident to the Parts of Generation, and their Treatment."

The next diseases are those that affect the private parts; the nomenclature of which among the Greeks is not only tolerable, but now fully sanctioned by practice; for they are freely employed in almost every volume, work, or treatise of the physicians: but with us Romans, these terms are certainly filthy, and never employed by anyone who has a proper regard for modesty in language: therefore it is evident from this explanation, that there is no small difficulty in maintaining at the same time a delicacy of expression while delivering the precepts of the art. Not that this circumstance ought to deter me from treating on them: first, because it is my intention to comprehend everything in this work which I have found to be conducive to health; in the next place, because every person ought to know the treatment of those maladies which we so reluctantly expose to the view of another.

If the advice set forth in this paragraph had been followed out through the ages down to the present time, how much further advanced would this subject be than is actually the case. Few qualities of the human temperament have delayed our knowledge of medicine more than that of false modesty and a tendency to conceal from the physician those things which he should know and which he should publish for the benefit of his successors in the profession.

One may see in the consideration of several conditions of which Celsus speaks a complete history of what we now call syphilis but which the author thought were different diseases. For instance, in Lib. VI, Cap. XVIII, p. 203 of Lee's edition, the hard and soft genital scores are quite accurately described. Under the disease called Porrigo, Lib. VI, Cap. II, p. 132, the author describes an alopecia which he says is always accompanied by an underlying dyscrasia. In Lib. VI, Cap. III, p. 133, Celsus describes "sycosis" and in his description it is evident that several diseases are confused, but one may easily see the same type of lesion which he describes for other parts of the body under the name of "ficus." It is the condyloma usually occurring between the nates in untreated syphilis. Then, with the discussion of ulcers of the palate, Lib. VI, Cap. II, p. 190, one may easily construct the symptomatology of syphilis which seems so evident from many other parts of his work.

In Lib. III, Cap. II, p. 182 occurs the following which seems as fresh as the morning dew. Under the "Treatment of Fever with Concomitant Symptoms" in the fourth paragraph occurs the following sentence—"Now there are four diagnostic marks of inflammation, *redness*, and *swelling*, with *heat*, and *pain*." In Lib. V, Cap. XXVII, pages 88 and 89, Celsus considers the treatment of snake bite and though he did not have any antivenene to help him out, his treatment of the condition is just about as satisfactory if not more effective than the present day attempts to use these antivenenes for the cure of snake bite. The treatment was the incision and cupping of the area bitten. As we know, at the present time the surgical treatment of snake bite as developed by

Jackson, Harrison and others is far more satisfactory than the treatment of the condition by biological products.

Professor E. R. Long in "Readings in Pathology," says that Books IV and V are particularly rich in pathological observation and that Book IV "is essentially a special pathology in which disease is considered in relation to the individual organs."

It is our belief that the wide spread knowledge of Celsus which will be available when the Loeb translation above referred to comes out, will give us a better perspective and greater respect for the men of our profession who lived in ancient times. Certainly it will take some of the pride out of present day practitioners to see what Celsus actually knew about disease and its treatment.

—C. S. BUTLER.

NEWS AND NOTICES

Twelfth Annual Convention of the American Society of Clinical Pathologists

June 9 to 12, 1932, Milwaukee, Wisconsin

The twelfth annual session of the American Society of Clinical Pathologists held in Milwaukee marks an epic in the history of the Society in its contribution to medical science in the field of medico-legal literature. The scientific program with its outstanding Symposium on the medico-legal necropsy was full of interest. From the opening paper to the closing one the audience was kept in constant attendance despite the excessive heat experienced during the sessions. The usual congregating outside of the meeting room during the scientific sessions was conspicuous by its absence. Needless to say the 138 members and sixty visitors attending the meeting were well repaid for their trip to Milwaukee despite the weather.

The Symposium on hematology was another outstanding feature in which the activities of the hematology Registry were reported by Dr. R. R. Kracke and brought to a climax by the excellent presentation of Dr. William Bloom which brought to the attention of every clinical pathologist the importance of tissue culture in the study of diseases of the hematopoietic system. Also this year the scientific program was well balanced by an excellent group of papers dealing with histopathology.

The committees on scientific and commercial exhibits were certainly well repaid for their efforts this year. The first award for scientific exhibits was made to the group exhibit presented by Drs. A. O. Gettler, H. S. Martland, C. Norris and A. V. St. George. This exhibit was intensely interesting as it illustrated graphically and by actual specimens an unusual variety of examples of lesions met with by those dealing with medico-legal

necropsies and also a graphic demonstration of the various agents producing such lesions. The second award was made to Dr. W. D. Stovall for an excellent exhibit demonstrating a new classification of fungi by bacteriologic and pathologic methods. The exhibits in pathologic anatomy were well chosen and presented including some rare specimens. Hematology was as usual well represented by a large series of demonstrations by slides and pictures done in natural color. The art of color photography was well illustrated in a beautiful series of slides personally prepared by Dr. O. Lohr.

The annual banquet was attended by over 200 members and visitors and was an outstanding feature of the meeting. Dr. N. Enzer acted as toastmaster and gave an excellent exhibit in the science of public speaking keeping the audience in unusually high spirits and handling the procedures of the meeting with a strategy possessed only by masters of the art. The presidential address "The Clinical Pathologist as Teacher and Consultant" given by Dr. W. M. Simpson was intensely interesting and no doubt will be read by every member. The annual Ward Burdick Award was presented at this time to Dr. A. H. Sanford of Rochester, Minnesota. Following extemporaneous remarks by Dr. M. T. MacEachern of the American College of Surgeons and Dr. W. D. Cutter of the American Medical Association, the evening address was presented by Mr. Joseph A. Padway on "A Lawyer Looks at the Medical Profession." This address is of sufficient interest to our membership and to the medical profession as a whole that it will be published together with the Symposium on the medicolegal necropsy.

The business session unfortunately was not well attended. It is hoped that in the future plans will be made so that the distraction caused by the other meetings taking place on this day will be avoided. The following are the minutes of the business session.

The business meeting of the Society was held at the Hotel Pfister on Monday, June 12th. The meeting was called to order by President W. M. Simpson. It was moved and seconded that the reading of the minutes be dispensed with since they had previously been published in the JOURNAL.

REPORT OF THE SECRETARY-TREASURER

Since the activities of the Society have been summarized from time to time by means of circular letters to the membership and news items published in the Journal and the separate Committees will report later on the activities of the Society, I will make my report very brief.

Your Secretary is very grateful for the splendid coöperation he has received from the various Committees and individual members. The President has been particularly active this year because of the numerous problems that have arisen. His leadership and untiring efforts deserve the unanimous gratitude of our membership. The response of the local Counsellors to his call for enlargement and improvement of our membership is well demonstrated by the number and type of applicants to our Society for this year. The total active membership is 353 up to June 1, 1933. Of these 280 have paid their annual dues, fifty-six are in arrears for the current dues, sixteen owe for two years and one for three years. Five members have resigned and sixteen have been suspended for non-payment of dues.

The financial status of the Society despite the past unfavorable conditions is slowly but surely growing as evidenced by the fact that the net worth of the Society in July of 1930 was $2696.00 as compared with the $4942.00 of June 1, 1933. This amount represents actual cash assets in bonds or cash in the bank. Of this amount $1638.43 is for the present unavailable due to the fact that the bank is being operated by a conservator. However I have been informed by reliable sources that the Society will not incur any losses on this amount.

Thanks to the coöperation of our membership in prompt payment of dues, the Society has been able to maintain its activities and still furnish each member with a year's subscription to our official Journal without increasing the dues despite the fact that the Journal costs the Society more than half the amount of the membership fee.

The following is a portion of the auditor's report:

BALANCE SHEET—MAY 29, 1933 AND STATEMENT OF INCOME AND EXPENSE FOR PERIOD FROM APRIL 20, 1932 TO MAY 29, 1933

Assets

Balance in Citizens National Bank—Current Account		$1,313.54
Investments:		
Commonwealth Edison Co., No. 41022, 4 per cent Gold Bond, Series F, Due March 1, 1981, Par Value $1,000.00	$945.00	
American Telephone & Telegraph Co., No. 70378, 5 per cent Col. Trust Gold Bond, Due December 1, 1946, Par Value $1,000.00	1,025.00	1,970.00
Furniture and fixtures	$601.75	
Less—Depreciation Reserve	581.21	20.54

Balance in Citizens National Bank:				
Withdrawals discontinued by order of Treas. Dept...				1,638.43
Total				$4,942.51
		Liabilities		
Balance Due Williams & Wilkins:				
Checks Issued prior to Bank Moratorium				$325.00
		Net Worth		
Balance—April 20, 1932			$4,363.06	
Income:				
Initiation Fees		$425.00		
Membership Dues		3,035.00		
Interest on Investments		91.92		
Commercial Exhibit		85.00		
Total		$3,636.92		
Expense:				
Salary	$650.00			
Office Expense	12.28			
Printing and Multigraphing	166.65			
Postage, Telephone and Telegraph	95.00			
Convention Expense	191.62			
Journal:				
Editorial Office	500.00			
Williams & Wilkins	1,510.00			
Loss on Bond	26.85			
Audit	41.00			
Bond	12.50			
Awards	47.72			
Safety Deposit Box Rent	3.30			
Miscellaneous	2.40			
Exchange	1.94			
Check Tax	.86			
Depreciation on Furniture and Fixtures	120.35	3,382.47		
Income in Excess of Expense			254.45	
Balance—May 29, 1933				4,617.51
Total				$4.942.51

Motion made and seconded for acceptance of report. Carried.

REPORT OF COMMITTEE ON PUBLIC RELATIONS

The relations of the clinical pathologist with the public are not simple, nor are they easily defined.

In other years we have tried to put into words our ideals of service; to clarify in our own minds our relations with the laity and with our fellow physicians, and

to correct by education and organization evils which we have seen were threatening the welfare of the profession. We have expressed our desire to serve as consultants; we have discouraged the control of clinical laboratories by technicians; we have deplored the doing by hospital laboratories of work in competition with independent clinical pathologists; and some of us have been disturbed by the encroachment of Public Health laboratories upon the diagnostic laboratory service which the practicing clinical pathologist is prepared to furnish.

One year ago your Committee on Public Relations, its chairman having had successful experience in opposing an overzealous State Laboratory, presented suggestions which were adopted by the Society, and were recommended to its Counsellors for use in the various States where State Laboratory competition was annoying.

Your present Committee believed that its first duty was to find out what had been done by the Society's Counsellors in carrying out the recommendations made last year. Letters addressed to each of the forty Counsellors brought twenty-six replies and a significant variety of information. The details given would extend this report beyond reason.

In several States the battle has been carried on vigorously. The methods have varied according to the local situations and the personality of the combatants.

In all of the States heard from the State Laboratories are, or have been, doing more or less diagnostic work, not limited to communicable diseases. Reduced appropriations for public health work have made retrenchments necessary, but the practicing physician wants to save expense for his hard-pressed patients. This tends to keep up the volume of work sent to State Laboratories and the directors say they dare not refuse to do work sent to them. Some of the States have a population so distributed that no private laboratory service is available for many communities and the State help is really needed. In still other commonwealths so many clinical pathologists have been forced out by State competition, or by other conditions, that the few who remain can keep profitably busy with types of service which cannot be given by technicians or by an impersonal laboratory.

Several reports indicate that State Medical Schools may tend to join forces with Public Health Departments, and influenced by common ambitions develop an embryonic form of State Medicine with free laboratory service an early result.

Two approaches to the problem have been used by those who agree that there is a problem. The militant pathologist uses his political or persuasive skill and tries to secure an executive or a legislative order restricting Public Health laboratory service or a Commission to supervise such service. This has been done successfully in Indiana and Dr. Rhamy has told the Society how it was done. California has solved its difficulties in a different manner. In at least three other States somewhat similar attempts have so far failed to get results. Groups of physicians avowedly opposed to and fearful of State Medi-

cine have nevertheless voted against measures which would curtail State Laboratory diagnostic services. Legislators and State executives are sometimes not sympathetic with measures designed to protect an unwilling electorate.

The non-militant fraction of the Counsellors reporting have favored, some very decidedly, a program of professional improvement for ourselves, and an educational program among the members of State Medical Societies. They argue that the improper use of State Laboratory facilities is due as much to the thoughtlessness or lack of vision of the physician who supplies the work, as to the desire of the laboratory director to increase his own opportunity for service.

The question remains a many-sided one. We are presenting, as a supplement to this report, a group of resolutions which, at the discretion of the Society's Counsellors may be used by them as a guide in presenting this subject to their State Medical Societies.

The American Society for the Control of Cancer has suggested that there should be in each State at least one tissue pathologist thoroughly competent to recognize malignancy. This suggestion implies, and correctly, that not all pathologists who undertake to diagnose tissues are expert in the recognition of malignancy. It also implies that someone is to certify to the competence of at least one surgical pathologist in each State. This Society is vitally interested in any measure which will insure an earlier and more accurate diagnosis of cancer and should be able to furnish and certify proper pathologists for tissue diagnosis. We should encourage thorough special training for tissue pathologists and a minimum amount of supervised experience before independent diagnoses are accepted.

Two of the States reporting already have Cancer Commissions, and one is doing much in offering training and encouragement to the practicing clinical pathologists. State or district pathological conferences modeled after those already being held in California can well be arranged in many parts of the country.

It is fitting to mention in this report the work done by the Committee on the Costs of Medical Care. The Committee in its report has given deserved recognition to the value of laboratory procedures as aids in diagnosis. It calls attention to the increasing use of the laboratory as the patient's economic status rises; and that the amount of laboratory aid used even by the most prosperous group falls far below the ideal. The majority report then goes on to state repeatedly that laboratory service is a proper public health function; to list "laboratory technicians" as an essential part of proposed free medical services; and to suggest that under the new deal the general practitioner "could continue his present functions in much the present method but would utilize extensively diagnostic clinics or State Laboratories." The first minority report in cautioning against the "constant temptation in many fields to permit technicians to perform duties entirely unjustified by their knowledge and training" agrees perfectly with the frequently expressed attitude of this Society.

Much emphasis has been placed upon a statement that it is laboratory

charges which make medical care cost more now than it did in the nineteenth century. This is at least partial truth. We believe that the added immediate expense often results in an ultimate saving. With medical economists hunting industriously for ways to fit proper medical care into the budgets of all economic groups, we will doubtless be compelled to work with them for a solution or else risk the forcing of arrangements made without our help. The public must be served.

As a definite program for our membership in its public relations we would recommend:

(1) The continued maintenance of the highest professional standards in our own work.
(2) The wise use of our influence to encourage legislation which will help preserve efficient laboratory service for the medical profession.
(3) Wider contacts between our members and other physicians to the end that they, as our associates, may know that as medical consultants and laboratory directors we are worthy of our hire.
(4) Active coöperation with all attempts to furnish more accurate tissue diagnosis.
(5) An official offer of coöperation by this Society in any organized plan for adjusting the economic side of medical care to the national budget.

RESOLUTIONS CONCERNING STATE LABORATORIES

WHEREAS, It is the recognized purpose of the Boards of Health of the various States to conserve the public health by measures for the prevention and control of communicable diseases, and

WHEREAS, Laboratories under the direction of many State Boards of Health have extended their activities beyond this field, for various reasons, and

WHEREAS, It is believed that the welfare of the public and of the medical profession will be best conserved if the activities of Public Health Laboratories are confined to measures for the prevention and regulation of communicable diseases, and to laboratory service for the indigent sick and for legal wards of the State,

Be It Resolved That two propositions be recommended for the consideration of State Medical Societies.

1. That the furnishing of general diagnostic service by State Laboratories tends to prepare the public conscience for the acceptance of added varieties of State medical practice.

2. That while the cost of true public health laboratory service is a legitimate governmental expense, the extension of this service into the field of general laboratory diagnosis is an unnecessary and unwarranted burden upon the taxpayers of the State.

These two points for criticism in the State Laboratory situation are very apparent in clinical pathologists and are worthy of consideration by the entire medical profession. It is unwise to ask the State to practice medicine in the

laboratory unless we are willing for it to spend still more public money and practice medicine in the ward and in the operating room.

The State Medical Societies can, and we believe they should, exert a powerful influence in keeping the demands made upon State Laboratories within the limits of truly public health functions. The Societies also can encourage the State Boards of Health to keep general diagnostic work out of their laboratories by regulation, and to inquire that each specimen from an indigent patient be accompanied by a card signed by both physician and patient. On this card the patient shall state: "I declare on my honor that I am financially unable to pay for this laboratory test and I know that the State Laboratory makes no charge for acid tests." The physician's statement shall read: "I state, on my honor, that this patient is financially unable to pay, and that I am making no charge for my services to this patient."

C. W. MAYNARD, *Chairman.*

Motion made and seconded for acceptance of report. Carried.

It was further moved and seconded that a copy of this report be sent to each Counsellor of the Society, the American Medical Association, the American Surgeons, American College of Physicians, Secretaries of the State Boards of Health and Directors of the State Boards of Health. Carried.

Moved and seconded that a letter be sent to the Presidents and Secretaries of the State Boards of Health who have contributed by their recent actions in the movement to withdraw services in the general field of clinical pathology and have attempted to restrict their activities to strictly public health problems. Carried.

REPORT OF EDITORIAL COMMITTEE

Volume 2 of the Journal has been completed in a satisfactory manner. As was thoroughly expected there was a falling off in subscriptions and advertising. Nevertheless, this was accomplished without the loss of good will and most cancellations have been due purely to financial conditions. In spite of this it was possible to furnish fifty extra pages and to make no charges for illustrations.

Owing to the record the Journal has made for the first two volumes the Williams and Wilkins Company is willing to set aside the original contract for the second time and as is shown in the enclosed letter has granted a more favorable contract to the Society. I recommend its adoption.

The Editor has been embarrassed by the necessity of returning dozens of manuscripts because of the lack of space in the Journal. It is also impossible to publish manuscripts as promptly as desired for the same reason. Nevertheless, until the financial situation clears up more, I recommend that no change in general policy be undertaken.

I invite the Executive Committee's attention to the necessity for the appointment of an editor and editorial board for the next three years beginning January 1, 1934.

T. B. MAGATH, *Chairman.*

Motion made and seconded for acceptance of report. Carried.

REPORT OF THE COUNCIL OF BIOLOGICAL ABSTRACTS

The meeting was held in Atlantic City with a very good attendance. The Editor reported excellent progress and support from the Rockefeller Foundation. A very unique and complete index to Volume II has been published and the other indices are now assured. Biological Abstracts has become extremely important in medical literature especially in pathology and is getting more so with each issue. The journal is to be strongly recommended to members of our Society.

T. B. MAGATH, *Representative.*

Motion made and seconded for acceptance of report. Carried.

REPORT OF THE BOARD OF REGISTRY

We submit herewith a report of the activities of the Registry for the twelve months ending April 30, 1933:

The past year has shown an unprecedent increase in the number of technicians applying for registration. No less than nine hundred have been added to our roster of which 893 were Laboratory Technicians and eleven received the classification of Medical Technologist. Our total registration now numbers 1949, and about 250 applications more are pending.

The phenomenal growth of the Registry and the increasing influence it exercises in medical and hospital circles are due to the cordial coöperation given us by the Fellows of the Society not only in having their own technicians registered but in giving freely of their time and labor in interviewing applicants referred to them for investigation. We have also been greatly aided in the hospital field by the representatives of the American College of Surgeons who, in their systematic inspection of hospitals, have emphasized the necessity of registering the laboratory workers under the auspices of the American Society of Clinical Pathologists. Similarly the American Medical Association has given the Registry recognition of its aims to maintain properly qualified laboratory technicians. The administrators of approved hospitals in the United States have likewise given us their support, as evidenced by their generous response to our circularization of over 2000 approved hospitals in the United States.

Our aims and purposes have been ably presented before the recent annual meeting of the Council on Medical Education and Hospitals by our President, Doctor Walter Simpson, and his address evoked useful discussion of the topic of technicians' training. This important adjunct to our work, the investigation and appraisal of schools for technicians, has been under the direct guidance of Doctor Kano Ikeda from whose report to our board we desire to make the following excerpts: On the basis of the minimum requirements for training technicians the total number of schools approved by the Board is 44. The great majority of these are conducted under the apprenticeship system in a hospital or private laboratory affiliated with a hospital of one hundred beds of over, and supervised by a competent clinical pathologist. Six of these schools are conducted by

colleges of higher learning who likewise have hospital affiliations. Here the students spend four years leading to a degree with medical technology as a major study. It is the endeavor of the Board to have all the approved training schools maintain a high level of instruction. Schools conducted primarily for profit are not eligible for approval.

During the year, we inaugurated the policy of publishing an official roster of the Laboratory Technicians and Medical Technologists who received certificates from our Board, also a list of approved schools for training technicians. This directory, arranged both alphabetically and geographically, serves a useful purpose for the technicians, the clinical pathologists and hospitals.

The Registry has also issued a revised edition of its booklet giving the aims and purposes of the Registry and defining the rules laid down by the Board for the qualification of technicians. Both of these pamphlets will be cheerfully sent to any of our Fellows on request.

In order to secure an unbiased appraisal of the technicians applying for certification, the Registry is inaugurating a written and oral examination to be conducted by a Fellow of our Society residing in the locality nearest to the applicant. The cooperation, heretofore shown by our colleagues, encourages us in the belief that they will gladly second our efforts in maintaining a high scientific and ethical standard of our registrants.

Appended herewith is the financial report of our Registry for the year 1932–1935, checked by a certified public accountant, which shows a very satisfactory condition of the treasury. All surplus above the working capital will, as in the preceding year, by vote of the Board be invested in Government Bonds.

In the conservation of these funds, the Board of Registry mindful of the altruistic aims of its foundation by the American Society of Clinical Pathologists, is looking ahead to the time when with the diminution of new applications the present surplus will enable the Registry to continue its useful function for the benefit of the patient, the technicians and the medical profession.

The Registry of Technicians since its inception in 1928 has become the recognized authority on this continent in evaluating the competence of laboratory technicians and training schools. Indirectly, it has also thrown into greater relief the important rôle of the clinical pathologist and enhanced the prestige of the American Society of Clinical Pathologists.

PHILIP HILLKOWITZ, *Chairman.*

Report accepted as read.

REPORT OF RESEARCH COMMITTEE

During the year, under the auspices of Dr. B. S. Kline, positive results obtained by use of the Friedman Test in cases of malignant testicular tumor, and also other cases were reported which gave a negative result with a rabbit. Also, positive tests were reported in cases of ectopic pregnancy with intact placental tissue, while three tubal pregnancies showing degenerated chorionic villi gave

negative tests, as is shown in the table below. The members of the Society used various technics, relative to quantity of urine injected and the number of injections and the duration of the test. The accuracy of the Friedman Test for normal pregnancies has been fully established, and it is suggested that future results of Society members in this regard be discontinued. A modification in technic worthy of note is the use of morphine sulphate intravenously as an anesthetic by Dr. A. M. Young, the details of which are in the Journal of Laboratory and Clinical Medicine (in press).

The Hematologic Registry under the care of Dr. R. R. Kracke now contains eighty cases of various types of blood dyscrasias, chiefly leukemias. Of these, twenty-eight cases are monocytic leukemias, collected by Dr. Kracke from the authors of the articles printed on the subject, including both American and foreign authors, the material of which collection was demonstrated at the Scientific Exhibit of our Society and the American Medical Association. It is hoped that more cases be sent in so that they may be loaned to the various men of the Society for their personal study.

There has been so little response to the subjects under the other divisions of our Committee, that details will be omitted here.

Your Committee wishes to thank the members who have cooperated in their work, and the President and Secretary of the Society, who have given their loyal support.

A. G. Foord, *Chairman.*

Report of Serology Division for 1932

The one matter dealt with in this division consisted in correspondence with Dr. A. S. Giordano, Secretary and Dr. W. M. Simpson, President of The American Society of Clinical Pathologists relating to a suggestion that a North American Serological Conference comparable to the League of Nations' Serological Conferences in Denmark and Uruguay be organized.

Inasmuch as several Wassermann technics and quite a number of flocculation tests developed in this country have not yet been tried under conditions of rigorous control as employed in The League of Nations' Serological Conferences, no definite conclusion as to their comparative value has been reached.

As stated by Professor J. Jadassohn, President of the last League of Nations' Serological Conference at Montevideo in 1931:

> The serological methods employed in the diagnosis of syphilis thus constitute a most valuable means of combating the disease. These methods deserve, therefore, our constant attention, and their improvement is of capital importance. Despite the merits of those who have already assisted in this work, the results are not yet entirely satisfactory, inasmuch as mathematical accuracy has not yet been achieved in connection with any one biological reaction. The fate of the patients depends, however, to a large extent upon the accuracy of these methods and, in connection with the diagnosis of syphilis in particular, a method must be found

which furnishes with syphilitic sera as high a percentage as possible of positive results, and does not produce non-specific reactions.

The various methods recommended have hitherto often been open to objection for one or other reason and sometimes produced inexplicably divergent results when used by the different serologists. The Laboratory Conferences on the serodiagnosis of syphilis convened by the League of Nations Health Organisation in 1923, 1928 and 1930 were intended to demonstrate the causes of these divergencies and to determine the value of different methods; the discussions also gave a definite impetus to serological researches, as may be seen by the improvement in methods, particularly flocculation methods during the last few years.

A North American Serological Conference, therefore, would be valuable in deciding the comparative merits of the various complement fixation and flocculation test methods employed in this country, Canada and Mexico and be helpful in establishing a high standard of procedure in the serodiagnosis of syphilis and in directing future research in this field.

In conclusion, it is recommended that the Society consider the advisability of organizing a North American Serological Conference.

B. S. KLINE.

Reports accepted as read.

REPORT OF THE COMMITTEE ON NECROPSIES

In a study of the matter of an insufficient number of autopsies in the various New York City hospitals, the Public Health Relations Committee of the New York Academy of Medicine found the cause to be in large part due to the existing Autopsy Law and the widespread practice of undertakers to advise against permission for postmortem examination.

While a change in the law was secured which was not as liberal as had been wished, it did however stop the claiming of bodies by undertakers in the hope of locating relatives or friends to pay funeral expenses, and the prevention by them of autopsies in these cases.

The matter of securing the goodwill of undertakers to stop as far as possible the practice of advising patrons against allowing postmortem examinations, was undertaken by a Joint Committee of the N. Y. Academy of Medicine, the New York Pathological Society and the Metropolitan Funeral Directors Association. A much improved understanding has resulted and autopsies are now much more general than formerly. The details are both interesting and instructive and will be published in the monograph on autopsies to be issued by the Society.

In view of the facts stated, your Committee recommends that this whole matter have the attention of pathologists generally with the hope that a postmortem examination can be more easily secured.

A. V. ST. GEORGE, *Chairman.*

REPORT OF THE BOARD OF CENSORS

A complete list of members approved and recommended by the board was published in the July issue of the JOURNAL.

It was moved and seconded that the President be empowered to appoint any Committee he sees fit during the ensuing year. It was particularly requested that a Committee be appointed for modification of the Constitution and By-Laws. Carried.

Motion duly seconded that a vote of thanks be extended to the Local Committee for a very enjoyable and profitable convention. Carried.

The meeting was adjourned at eleven-thirty A.M.

A. S. GIORDANO, *Secretary-Treasurer.*

The following Committees have been appointed:

Committee on Local Arrangements:
B. S. Kline, Chairman
Anna M. Young
Russell Haden

Program Committee:
A. S. Giordano, Chairman
Frank Heck
W. M. Simpson

Scientific Exhibit Committee:
Russell Haden, Chairman
W. S. Thomas
H. C. Sweany

Constitution Revision Committee:
J. H. Black, Chairman
W. S. Thomas
K. M. Lynch

Necrology Committee:
J. J. Moore, Chairman
Herman Spitz
F. C. Payne

Committee on Necropsies:
F. E. Sondern, Chairman
I. Davidsohn
S. P. Reimann

Publication Committee:
J. A. Kolmer, Chairman
Kano Ikeda
W. C. MacCarty

Public Relations Committee:
C. W. Maynard, Chairman
K. M. Lynch
B. W. Rhamy

Round Table Committee:
F. H. Lamb, Chairman
J. H. Black
J. J. Moore

Publicity Committee:
T. B. Magath, Chairman
A. S. Giordano
W. M. Simpson

Research Committee
R. R. Kracke, General Chairman

(1) Hematology Division:
R. R. Kracke, Chairman
Frank Heck
N. Rosenthal

(2) Tumor Registry:
O. A. Brines, Chairman
A. C. Broders
C. M. Hyland

(3) Slide Exchange:
N. Enzer, Chairman

(4) Serology and Hormone Tests:
B. S. Kline, Chairman

Registry of Technicians of the American Society of Clinical Pathologists

The Board of Registry of the American Society of Clinical Pathologists at its annual meeting, in Milwaukee, on June 8th, 1933, considered eighty-four applications for the advanced rating of Medical Technologist. After careful examination of each applicant's qualifications thirty-seven were granted this title.

The question of training schools for laboratory technicians was uppermost in the minds of the Board who had previously gone on record against acceptance of applications from commercial schools. The ultimate goal of the Board is to place the training of clinical laboratory technicians under the tutelage of universities and colleges of learning. At present, clinical pathologists with good hospital affiliations may take on a limited number of students for training under the apprenticeship system.

The American Society of Clinical Laboratory Technicians was organized in Chicago, June 12–13, 1933. The meeting was opened at 2:30 P.M., June 12, with an invocation by Rev. A. J. Cook, S.J., of Cook County Hospital, Chicago. This was followed by an address of welcome by Dr. J. J. Moore, Director of the National Pathological Laboratory, Chicago, and an illustrated lecture on Diseases of the Blood by Dr. Roy R. Kracke, Department of Pathology, Emory University, Georgia. Ten states were represented by delegates, and six others by proxy.

Officers elected were: President, Miss Madge Baldwin, Illinois; President Elect, Miss Lucille Burns, Minnesota; Vice President, Miss Elizabeth Gambrill, Georgia; Secretary-Treasurer, Mr. Donald S. Bryant, Illinois.

A banquet was held at the Medinah Athletic Club, at 7:30 P.M., at which Dr. Philip Hillkowitz, Chairman of the Board of Registry, Denver, Colorado, gave an address on registration, followed by Dr. Kano Ikeda, Secretary of the above Board, giving a history of the Registry and the requirements for registered technicians and medical technologists. Dr. J. J. Moore served as master of ceremonies. The program was enlivened by vocal solos, readings, and folk dances.

All registered technicians are invited and urged to become members. This may be done by getting in touch with your local society, or with Mrs. Louise R. Wright, 4535 East 17th Avenue, Denver, Colorado.